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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF

THE NATIONAL INSTITUTES OF HEALTH AND

THE CENTERS FOR DISEASE CONTROL

AND PREVENTION

FOR

SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE

NOVEMBER 7, 2011

Internet: http://grants.nih.gov/grants/funding/sbir.htm

TABLE OF CONTENTS

PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)

APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD - USE FOR PHASE II AND FAST-TRACK PROPOSALS

MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc)
PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)

The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

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U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE NATIONAL INSTITUTES OF HEALTH AND THE CENTERS FOR DISEASE CONTROL AND PREVENTION FOR SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PART I INSTRUCTIONS FOR PREPARING AND SUBMITTING A PROPOSAL

1. PROGRAM DESCRIPTION

1.1 PURPOSE OF SOLICITATION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns to submit research proposals under this Small Business Innovation Research (SBIR) Contract Solicitation. Firms with the capability to conduct research and development (R&D) in any of the health related topic areas described in Section 12, and to commercialize the results of that R&D, are encouraged to participate.

This solicitation is for Phase I contract proposals and also for Phase I/Phase II Fast-Track contract proposals (see specific topics listed in Section 12 and awarding components identified as accepting Fast-Track proposals).

Included are instructions for offerors to prepare contract proposals, a description of the proposal review process, and some conditions of a contract award. **Contract proposals will be accepted only if they respond specifically to a research topic within this solicitation (see Section 12 "Research Topics").** Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR GRANT rather than an SBIR CONTRACT, use the Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Applications (http://grants.nih.gov/grants/guide/pa-files/PA-11-096.html).

The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal R/R&D needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The Federal SBIR program is authorized under Public Laws 97-219, 99-443, 102-564, and 106-554. The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive, 2002. This SBIR Contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components shown in Section 1.3. The guidelines presented in this solicitation reflect the flexibility provided in the Policy Directive to encourage proposals based on scientific and technical approaches most likely to yield results important to the NIH/CDC and to the private sector.

1.2 THREE PHASE PROGRAM

The SBIR program consists of three separate phases:

Phase I: Feasibility; $150,000; 6 months

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further

Federal support in Phase II. Phase I awards normally may not exceed $150,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort; $1,000,000; 2 years

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. Phase II awards normally may not exceed $1,000,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed two years. *Phase II proposals may only be submitted upon the request of the Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section 5). Only one Phase II award may result from a single Phase I SBIR contract.*

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR funds the commercialization objectives resulting from the outcomes of the research or R&D funded in Phases I and II. Phase III may involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR award, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5 that the project is a SBIR Phase III award that is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

The NIH is interested in developing products and services via the SBIR program that improve the health of the American people. In its commitment to also support former President Bush's Executive Order 13329, encouraging innovation in manufacturing-related research and development, NIH seeks, through the SBIR program, biomedical research related to advanced processing, manufacturing processes, equipment and systems; or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the NIH Small Business Research Funding Opportunities Web site and in the NIH Guide for Grants and Contracts as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers".

1.3 AWARDING COMPONENTS

The following awarding components are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH)

- National Cancer Institute (NCI)
- National Center for Research Resources (NCRR)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute on Drug Abuse (NIDA)

Centers for Disease Control and Prevention (CDC)

- Center for Global Health (CGH)
- National Center for Birth Defects and Developmental Disabilities (NCBDDD)

- National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)
- National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)
- Office of Public Health Preparedness and Response (OPHPR)

1.4 SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern as defined in Section 3. In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 CFR 121.103, affiliation exists when "… one concern controls or has the power to control the other … control may be affirmative or negative, …it does not matter whether control is exercised, so long as the power to control exists." One of the circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 CFR 121.103 also states that control or the power to control exists when "… key employees of one concern organize a new concern … and serve as its officers, directors, principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise." Where there is indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Joint ventures and limited partnerships are eligible provided the entity created qualifies as a small business concern as defined in Section 3 of this solicitation.

If it appears that an offeror does not meet eligibility requirements, the NIH/CDC will request an eligibility determination of the organization from the cognizant SBA Government Contracting Area Office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination.

Project Director/Principal Investigator Criteria. The primary employment of the Project Director/Principal Investigator (PD/PI) must be with the offeror at the time of contract award and during the conduct of the proposed project. The PD/PI is the single individual designated in the proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the PD/PI's time* is spent in the employ of the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization*.

In the event that the PD/PI: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility*. If the PD/PI also is employed or appears to be employed by an organization other than the offeror (e.g., a university, a nonprofit research institute, or another company), a letter must be provided by the *non-offeror organization* confirming that the PD/PI will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the PD/PI is employed by a university, the Dean's Office must provide such a letter. If the PD/PI is employed by another for-profit organization, the corporate official must sign the letter. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

Multiple Principal Investigators. Offerors may propose a multiple Project Director/Principal Investigator (PD/PI) model to direct the project or program to be supported by the contract. The multiple PD/PI model is intended to supplement, and not replace, the traditional single PI model. Ultimately, the decision to submit a proposal using the multiple PD/PI versus single PD/PI is the decision of the investigators and their organizations. The decision whether to employ multiple PDs/PIs should be consistent with and justified by the scientific goals of the project.

The offeror organization may designate multiple individuals as principal investigators (PD/PIs) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the offeror organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on a proposal or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

For Multiple PD/PI proposals: The first PI listed must be affiliated with the small business concern organization submitting the proposal and will serve as the **Contact PD/PI**. For both SBIR Phase I and SBIR Phase II, the *primary employment of the "Contact PD/PI" must be with the small business concern at the time of award and during the conduct of the proposed project.*

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States (see* Part I, Section 3. Definitions*)*.

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project.* It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

Market Research. *The NIH/CDC will not support any market research under the SBIR program*. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable.

For purposes of the SBIR program, "market research" is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, "market research" does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

2. AGENCY CONTACT FOR INFORMATION

Web Site. The NIH SBIR/STTR Web site at http://grants.nih.gov/grants/funding/sbir.htm offers electronic access to SBIR solicitations, abstracts of ongoing SBIR projects, the latest updates on the SBIR program, hyperlinks to sources of business assistance, and other useful information.

Technical Questions about Solicitation Topics or Contract Administration. Technical questions about a particular contract topic and general questions on the administration of an SBIR contract should be directed to the appropriate contracting officer listed in Section 10. Contracting Officers and Addresses for Mailing and Delivery of Proposals.

General Questions about the NIH SBIR Program

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General Questions about the CDC SBIR Program

Juliana Cyril, Ph.D., M.P.H.
Deputy Director, Office of Science Quality
Office of the Associate Director for Science
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Listserv. The NIH maintains a ListServ e-mail broadcast service. To stay in touch with SBIR opportunities and receive notices about upcoming conferences and solicitations, subscribe by sending an e-mail to LISTSERV@LIST.NIH.GOV with the following text in the message body: subscribe listname your name, where listname is the name of the list you wish to subscribe to, and your name is your name. (LISTSERV will get your e-mail address from the "From:" address of your e-mail message.)

3. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 CFR part 121 – Small Business Size Regulations, §121.103, *"What is affiliation?"*

Autopsy Materials. The use of autopsy materials is governed by applicable Federal, state and local law and is not directly regulated by 45 CFR part 46.

Child. The NIH Policy on Inclusion of Children defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific or ethical reasons not to include them.

DHHS Regulations (45 CFR part 46, Subpart D, Sec.401-409 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd)) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a "child." Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as research with human subjects that is:
(1) Patient-Oriented Research.
Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical studies, or (d) development of new technologies.

(2) Epidemiologic and Behavioral Studies.

(3) Outcomes Research and Health Services Research.

Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a clinical trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial*. For the purpose of the Guidelines an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Coded. With respect to private information or human biological specimens, *coded* means that:

(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and

(2) a key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

Research that involves only coded private information/data or coded human biological specimens may not constitute human subjects research under the DHHS human subjects regulations (45 CFR 46) if:

- the specimens and/or information/data are not obtained from an interaction/intervention with the subject specifically for the research; and
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited).

Individuals who provide coded information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

(See the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: http://www.hhs.gov/ohrp/policy/cdebiol.html.)

Commercialization. The process of developing markets and producing and delivering products for profit (whether by the originating party or by others). As used here, commercialization includes both government and private sector markets.

Consultant. An individual who provides professional advice or services for a fee, but normally not as an employee of the engaging party. In unusual situations, an individual may be both a consultant and an employee of the same party, receiving compensation for some services as a consultant and for other work as a salaried employee. To prevent apparent or actual conflicts of interest, grantees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

Contract. An award instrument establishing a binding legal procurement relationship between a funding agency and the recipient, obligating the latter to furnish an end product or service and binding the agency to provide payment therefore.

Data and Safety Monitoring Plan. For each clinical trial, NIH requires a data and safety monitoring plan that will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the contractor's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html).

Data and Safety Monitoring Board (DSMB). NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, *and generally for Phase III clinical trials*.

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one contract proposal or grant application submitted to the same Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Exemptions. The six categories of research exempt from the DHHS human subject regulations are:

Exemption 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (see 45 CFR part 46, Subpart D (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd)), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 3: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html) of the Office for Human Research Protection (OHRP) will determine whether the research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. The NIH Office of Extramural Research Web site also contains information that is helpful for determining whether human subjects research meets the criteria for Exemption 4. See http://grants.nih.gov/grants/policy/hs/index.htm.

Research that meets the criteria for Exemption 4 is not considered “clinical research” as defined by NIH. Therefore the NIH policies for inclusion of women, minorities and children in clinical research, and targeted/planned enrollment tables, do not apply to research projects covered by Exemption 4.

Exemption 5: Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs (ii) procedures for obtaining benefits or services under those programs (iii) possible changes in or alternatives to those programs or procedures or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Exemption 6: Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Feasibility. The extent to which a study or project may be done practically and successfully.

Funding Agreement. Any grant, contract, or cooperative agreement entered into between any Federal agency and any small business concern for the performance of experimental, developmental, or research work, including products or services, funded in whole or in part by the Federal Government.

Gender. Refers to the classification of research subjects into either or both of two categories: male and female. In some cases, representation is unknown, because gender composition cannot be accurately determined (e.g., pooled blood samples or stored specimens without gender designation).

Human Subjects. The DHHS regulations "Protection of Human Subjects" (45 CFR part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html), administered by OHRP) define a human subject as a living individual about whom an investigator conducting research obtains:

- data through *intervention* or *interaction* with the individual or
- identifiable *private information*

Individually Identifiable Private Information. According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Innovation. Something new or improved, including research for: (1) development of new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For the purposes of PHS programs, an example of "innovation" would be new medical or biological products for improved value, efficiency, or costs.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as "intellectual property," including but not limited to: patents, trademarks, copyrights, trade secrets, SBIR technical data (as defined in this section), ideas, designs, know-how, business, technical and research methods, and other types of intangible business assets, and including all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR program.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 CFR 46.102(f)).

Interaction includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102(f)).

Investigator. The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. (See OHRP's Guidance on Research Involving Coded Private Information on Biological Specimens: http://www.hhs.gov/ohrp/policy/cdebiol.html.)

Joint Venture. An association of concerns with interests in any degree or proportion by way of contract, express or implied, consorting to engage in and carry out a single specific business venture for joint profit, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. A joint venture is viewed as a business entity in determining power to control its management.

Manufacturing-related R&D as a result of Executive Order 13329. Encompasses improvements in existing methods or processes, or wholly new processes, machines or systems. Four main areas include:

1. *Unit process level technologies* that create or improve manufacturing processes including:
    - fundamental improvements in existing manufacturing processes that deliver substantial productivity, quality, or environmental benefits.
    - development of new manufacturing processes, including new materials, coatings, methods, and associated practices.
2. *Machine level technologies* that create or improve manufacturing equipment, including:
    - improvements in capital equipment that create increased capability (such as accuracy or repeatability), increased capacity (through productivity improvements or cost reduction), or increased environmental efficiency (safety, energy efficiency, environmental impact).
    - new apparatus and equipment for manufacturing, including additive and subtractive manufacturing, deformation and molding, assembly and test, semiconductor fabrication, and nanotechnology.
3. *Systems level technologies* for innovation in the manufacturing enterprise, including:
    - advances in controls, sensors, networks, and other information technologies that improve the quality and productivity of manufacturing cells, lines, systems, and facilities.
    - innovation in extended enterprise functions critical to manufacturing, such as quality systems, resource management, supply change integration, and distribution, scheduling and tracking.
    - technologies that enable integrated and collaborative product and process development, including computer-aided and expert systems for design, tolerancing, process and materials selection, life-cycle cost estimation, rapid prototyping, and tooling.
4. *Environment or societal level technologies* that improve workforce abilities, productivity, and manufacturing competitiveness, including:
    - technologies for improved workforce health and safety, such as human factors and ergonomics.
    - technologies that aid and improve workforce manufacturing skill and technical excellence, such as educational systems incorporating improved manufacturing knowledge and instructional methods.

Obtains. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:

(a) observing or recording private behavior;

(b) using studying, or analyzing for research purposes identifiable private information or identifiable specimens provided to investigators from any source; and

(c) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

Principal Investigator, Program Director, or Project Director (PD/PI). The individual(s) designated by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award. The applicant organization may designate multiple individuals as principal investigators (PDs/PIs) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the applicant organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on an application or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is

or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 CFR 46.102(f))

Prototype. A model of something that is to be further developed and includes designs, protocols, questionnaires, software, and devices.

Research or Research and Development (R/R&D). Any activity that is:

- A systematic, intensive study directed toward greater knowledge or understanding of the subject studied; or
- A systematic study directed specifically toward applying new knowledge to meet a recognized need; or
- A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

SBIR Technical Data. All data generated during the performance of an SBIR award.

SBIR Technical Data Rights. The rights a small business concern obtains in data generated during the performance of any SBIR Phase I, Phase II, or Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

Senior/Key Personnel. The PD/PI and other individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries or compensation are requested under the contract.

Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of senior/key personnel. Consultants and those with a postdoctoral role should also be included if they meet the definition of senior/key personnel. Senior/key personnel must devote measurable effort to the project whether or not salaries or compensation are requested--"zero percent" effort or "as needed" are not acceptable levels for those designated as senior/key personnel.

Significant Difference. For purposes of NIH policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

Small Business Concern. A concern that, on the date of award for both Phase I and Phase II funding agreements:

1. is organized for profit, with a place of business located in the United States, which operates primarily within the United States or which makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor;
2. is in the legal form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust or cooperative, except that where the form is a joint venture, there can be no more than 49 percent participation by foreign business entities in the joint venture;
3. is at least 51 percent owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States, except in the case of a joint venture, where each entity to the venture must be 51 percent owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States; and
4. has, including its affiliates, not more than 500 employees.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 CFR 121, as is the process for calculating "number of employees."

Business concerns include, but are not limited to, any individual (sole proprietorship), partnership, corporation, joint venture, association, or cooperative. Further information may be obtained by contacting the Small Business Administration Size District Office at http://sba.gov/size.

Socially and Economically Disadvantaged Individual. A member of any of the following groups: Black Americans; Hispanic Americans; Native Americans; Asian-Pacific Americans; Subcontinent Asian Americans; other groups designated from time to time by the Small Business Administration (SBA) to be socially disadvantaged; or any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act, 15 U.S.C. 637(a).

Socially and Economically Disadvantaged Small Business Concern. A socially and economically disadvantaged small business concern is one that is at least 51% owned by (a) an Indian tribe or a native Hawaiian organization, or (b) one or more socially and economically disadvantaged individuals; **and** whose management and daily business operations are controlled by one or more socially and economically disadvantaged individuals.

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The 50 states, territories and possessions of the U.S., Commonwealth of Puerto Rico, Trust Territory of the Pacific Islands, and District of Columbia.

Women-Owned Small Business Concern. A small business concern that is at least 51% owned by a woman or women who also control and operate it. "Control" in this context means exercising the power to make policy decisions. "Operate" in this context means being actively involved in the day-to-day management.

4. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

4.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals shall not exceed 50 single-sided, single-spaced pages for the entire proposal, all inclusive [including all pages, cover sheet(s), tables, CVs, resumes, references, pictures/graphics, and all enclosures, appendices or attachments, etc.]. Proposal pages shall be numbered "Page 1 of 50," "Page 2 of 50," and so on. Pages shall be of standard size (8.5" X 11") with a font size of 11 points (or larger). Two sided pages count as two pages. There are NO exclusions to the page limit – the complete proposal shall not exceed 50 pages. Pages in excess of the page limitation will be removed from the proposal and will not be read, considered, or evaluated.

4.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

4.2.1 Technical Proposal Cover Sheet - Complete the form identified as Appendix A (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)), and use it as the first page of the proposal. *No other cover sheet should be used*.

If submitting a proposal reflecting Multiple Project Directors/Principal Investigators (PDs/PIs), the individual designated as the Contact PI should be entered here.

- ***Topic Number.*** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (A numerical or alphabetical designator precedes each topic and subtopic.)

- ***Project Title.*** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the solicitation.

4.2.2 Abstract of Research Plan - Complete the form identified as Appendix B (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)), and insert it as the second page of each proposal. Do not include any proprietary information as abstracts of successful proposals will be published by NIH. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research.

Include at the end of the Abstract a brief description (two or three sentences) of the relevance of this research to **public** health. In this description, be succinct and use plain language that can be understood by a general, lay audience.

4.2.3 Research Plan

Beginning on page three of the proposal, discuss in the order indicated the following elements:

a. ***Identification and Significance of the Problem or Opportunity.*** Provide a clear statement of the specific technical problem or opportunity addressed.

b. ***Technical Objectives.*** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.

c. ***Work Plan.*** Provide an explicit, detailed plan for the Phase I R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address how the objectives will be met and the questions stated in Item b above. Discuss in detail the methods to be used to achieve each objective or task. The plan should indicate what is planned, how, when, and where the work will be carried out, a schedule of major events, the final product to be delivered, and the completion date of the effort. The Phase I effort should determine the technical feasibility of the proposed concept. For specific guidance and instructions related to Human Subjects research, please see the section entitled, "Human Subjects Research and Protection from Risk" and the "Human Subjects Research Guidance and Information Supplement."

d. ***Related Research or R&D.*** Describe significant research activities directly related to the proposed effort, including any conducted by the Project Director/Principal Investigator (PD/PI), the proposing firm, consultants, or others. Describe how these activities interface with the proposed project and discuss any planned coordination with outside sources. *The PD/PI must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field*.

e. ***Relationship with Future R&D.***

   1. State the anticipated results of the proposed approach, assuming project success.

   2. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

f. ***Potential Commercial Applications.*** Describe why the proposed project is deemed to have potential commercial applications (for use by the Federal Government and/or private sector markets.) Describe the market as it currently exists and how your product may enter and compete in this market. Include the potential barriers to market entry and how you expect to overcome them.

g. ***Senior/Key Personnel and Bibliography of Directly Related Work.*** Identify senior/key personnel, including their directly related education, experience, and bibliographic information. Where resumes are extensive, focus on summaries of the most relevant experience or publications. *Provide dates and places of employment* and some information about the nature of each position or professional experience. Resumes must identify the current or most recent position.

   Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving

conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

h. ***Subcontractors/Consultants.*** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters from each individual confirming his/her role in the project must be included. Small business concerns must perform a minimum of two-thirds for Phase I of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

i. ***Facilities and Equipment.*** Indicate where the proposed research will be conducted. *One of the performance sites must be the offeror organization*. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project*. It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

Title to Equipment. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property.

Any research proposal involving the collection of information, such as surveys or interviews, of 10 or more public respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

4.2.4 Current Awards and Pending Proposals/Applications

A small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or different awarding component(s) of the NIH/CDC. The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for award. A firm that receives a Phase I SBIR contract may submit a Phase II grant application and vice versa.

A Phase I contractor may submit a Phase II contract proposal only if invited by an NIH Contracting Officer.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this solicitation) for consideration under numerous Federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort.

If there is any question concerning this, it must be disclosed to the soliciting agency or agencies before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, include a statement in each such proposal indicating the information requested in items a-j set forth below.

In addition, provide the information requested in items a-j on (1) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (2) contract proposals and grant and cooperative agreement applications pending review or funding; and (3) contract proposals and grant and cooperative agreement applications about to be submitted.

a. Name and address of the funding source.

b. Type of award (contract, grant, cooperative agreement) and identifying number.

c. Title of research project.

d. Name and title of Principal Investigator(s) or Project Manager(s).

e. Hours per week on the project by the Principal Investigator(s) or Project Manager(s).

f. Annual costs proposed or awarded.

g. Entire period of support.

h. Date of proposal/application submission or date of award.

i. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.

j. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR*.

4.2.5 Prior SBIR Phase II Awards

If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II.

This information must be submitted with the proposal.

4.2.6 Proposed Cost Breakdown

Complete the form identified as Appendix C (Contract Pricing Proposal) (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed*.

- Under “Government Solicitation No.,” enter “PHS 2012-1.”
- If supplies are proposed, provide the quantities and the price per unit.
- Under “Direct Labor,” *list all senior/key personnel by name*. Support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.
- Cost for travel funds must be justified and related to the needs of the project. If travel is proposed, provide the following details on “Exhibit A – Supporting Schedule”: destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown as required for Appendix C. *Also provide a copy of the subcontractual agreement*.

- Use "Exhibit A – Supporting Schedule" to itemize and justify all major cost elements. If more space is needed, use Page 3 of Appendix C.
- Small business concerns must perform a minimum of two-thirds of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

4.2.7 Streamlining the Contracting Process

The NIH uses special *"Just-in-Time" procedures* that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the "Just-in-Time" procedures and offerors who elect to submit proposals under the *"Fast-Track" initiative* below are not required to submit this documentation with their initial Phase II business proposal:

- ***Travel Policy.*** The offeror's written travel policy.
- ***Annual Financial Report.*** The offeror's most recent annual financial report.
- ***Total Compensation Plan.*** Salary and fringe benefits of professional employees under service contracts.
- ***Data Substantiating the Costs and Prices Proposed.*** That is, payroll documentation, vendor quotes, invoice prices, etc.

4.2.8 Requirement for Adequate Assurance of Protection of Human Subjects

The DHHS regulations for the Protection of Human Subjects, 45 CFR 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. *The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections (OHRP), DHHS (*http://www.hhs.gov/ohrp*) before a DHHS award can be made.*

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

Human Subjects Research and Protection from Risk

Instructions and Required Information

This information must be submitted with the proposal.

Create a section heading entitled "**Human Subjects Research**." Place it immediately following the "Research Plan" section of the proposal.

In the Human Subjects Research section, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html)), (2) the requirements of NIH policies for data and safety monitoring of clinical trials, and (3) the requirements of NIH policies on inclusion of women, minorities, and children.

Provided in the Human Subjects Research Guidance and Information Supplement are six possible research scenarios, and links to the instructions for providing information on human subjects protection information and the inclusion of women, minorities, and children specific to each scenario. All research will fall into one of these six scenarios. Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in Section 3 of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3,

Definitions. Section 5 of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

Much of the information on the protection of human subjects that you are required to provide in this section is identical to information that will be required for IRB review.

4.2.9 Requirement for Adequate Assurance of Compliance with the PHS Policy on Humane Care and Use of Laboratory Animals

Instructions and Required Information

This information must be submitted with the proposal.

Create a section heading entitled **"Vertebrate Animals."** Place it immediately following the "Research Plan" section of the proposal (or after Human Subjects Research section, if applicable).

Under the Vertebrate Animals heading, address the following five points. In addition, when research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the proposal, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (http://grants.nih.gov/ grants/guide/notice-files/NOT-OD-02-064.html).

In August, 2002 NIH announced an IACUC "Just-in-Time" process for applications submitted for the October 1, 2002 deadline or other deadlines where the applications had a May/June 2003 Council review. The PHS policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. The new policy gave institutions flexibility in the timing of IACUC review relative to the submission of a proposal and the verification of IACUC review. The policy does not require that IACUC approval be deferred. Institutional officials retain the discretion to require IACUC approval prior to NIH peer review in circumstances of their choosing if deemed necessary. As part of the NIH peer review process, the scientific review group will continue to address the adequacy of animal usage and protections in the review of a proposal and will continue to raise any concerns about animal welfare issues. Verification of IACUC approval will be required in a "Just-in-Time" fashion prior to award.

The *PHS Policy on Humane Care and Use of Laboratory Animals* requires that offeror organizations proposing to use vertebrate animals file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS policy stipulates that an offeror

organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program. This policy does not affect applicable state or local laws or regulations that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 U.S.C. 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

The PHS Policy defines “animal” as “any live, vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes.”

No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with the PHS policy. Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

4.3 LIMITATIONS ON USE OF APPROPRIATED FUNDS

The Department of Health and Human Services Appropriation Act for Fiscal Year 2010 (Public Law 111-117), limits the use of appropriated funds on NIH grant, cooperative agreement, and contract awards for Fiscal Year 2010, as specified below. It is anticipated that these statutory provisions will continue in subsequent fiscal years.

Salary Rate Limitation

For FY 2011, the Department of Defense and Full year Continuing Appropriations Act of 2011 (Public Law 112-10) continues implementation of Public Law 111-117: Consolidated Appropriations Act, 2010 which restricts the amount of direct salary to Executive Level I of the Federal Executive Pay scale. No increase has been provided for Federal salaries. Therefore the Executive Level I salary level remains at $199,700 which will be the salary limitation for the remainder of FY2011.

Anti-Lobbying

"(a) No part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself. (b) No part of any appropriation contained in this Act shall be used to pay the salary or expenses of any grant or contract recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature."

Restriction on Distribution of Sterile Needles

"None of the funds contained in this Act may be used to distribute any needle or syringe for the purpose of preventing the spread of blood borne pathogens in any location that has been determined by the local public health or local law enforcement authorities to be inappropriate for such distribution."

Acknowledgment of Federal Funding

"When issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money, all grantees receiving Federal funds included in this Act, including but not limited to State and local governments and recipients of Federal

research grants, shall clearly state: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) percentage and dollar amount of the total costs of the project or program that will be financed by non-governmental sources."

Restriction on Abortions

"(a) None of the funds appropriated under this Act, and none of the funds in any trust fund to which funds are appropriated in this Act, shall be expended for any abortion. (b) None of the funds appropriated in this Act, and none of the funds in any trust to which funds are appropriated in this Act, shall be expended for health benefits coverage that includes coverage of abortions. (c) The term "health benefits coverage" means the package of services covered by a managed care provider or organization pursuant to a contract or other arrangement."

Ban on Funding of Human Embryo Research

"(a) None of the funds made available in this Act may be used for: (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, the term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."

Limitation on Use of Funds for Promotion of Legalization of Controlled Substances

"(a) None of the funds made available in this Act may be used for any activity that promotes the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established by section 202 of the Controlled Substances Act except for normal and recognized executive-congressional communications. (b) The limitation in subsection (a) shall not apply when there is significant medical evidence of a therapeutic advantage to the use of such drug or other substance or that federally sponsored clinical trials are being conducted to determine therapeutic advantage."

NIH Public Access Requirement

"The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: *Provided*, that the NIH shall implement the policy in a manner consistent with copyright law."

Further information on the implementation of NIH's Public Access Requirement is available in NIH Guide Notice NOT-OD-08-033 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html) published on January 11, 2008.

Dissemination of False or Deliberately Misleading Scientific Information

"None of the funds made available in this Act may be used to disseminate scientific information that is deliberately false or misleading."

While this mandate has not been included in past appropriations acts, it is similar to existing requirements concerning research integrity, fraud, and false claims, and as such, NIH does not expect this new requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their implementation of the PHS Policies on Research Misconduct contained in 42 CFR Part 93 and the Civil False Claims Act (31 U.S.C. 3729(a)), Criminal False Claims Act (18 U.S.C. 287 and 1001), and Program Fraud and Civil Remedies Act (31 U.S.C. 3801 et seq.).

Restriction on Employment of Unauthorized Alien Workers

"None of the funds in this Act may be used to employ workers described in section 274A(h)(3) of the Immigration and Nationality Act."

While this mandate has not been included in past appropriations acts, it is similar to existing requirements contained in the Immigration and Nationality Act (18 U.S.C. 1324a), and as such, NIH does not expect this new requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their current hiring and employment practices to ensure compliance.

5. "FAST-TRACK" INITIATIVE

(Applicable Only to Proposals Submitted to NIH)

The "Fast-Track" initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast-Track proposals for a particular topic. (Refer to Section 12. "Research Topics," for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Phase I and Phase II are considered separate funding agreements under the Fast-Track Initiative. Therefore, Phase I Fast-Track awardees must recertify that they meet all of the eligibility criteria for an SBIR award prior to issuance of the Phase II award.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked "Yes" next to the words "Fast-Track Proposal" shown on the Phase I Proposal Cover Sheet, Appendix A (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. ***Phase I Proposal.*** Prepared in accordance with Section 4. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section 7) for Phase I proposals.
2. ***Phase II Proposal.*** Prepared in accordance with Section 6, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section 7) for Phase II proposals.
3. **Commercialization Plan.** Prepared in accordance with instructions in Section 6.2.

The Phase I and Phase II proposals are separate proposals and will be scored individually.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were met, feasibility was demonstrated, and funds are available.

6. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

6.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals shall not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8.5" x 11") with a font size of 11 points (or larger). Excluded from

the page limitation are cover letters and letters from collaborators and consultants. Pages in excess of the page limitation will be removed from the proposal, and will not be read, considered, or evaluated.

6.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf)).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**
   a. *Detailed Approach and Methodology* - provide an explicit detailed description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract. Offerors using Human Subjects or Vertebrate Animals in their research should refer to the specific instructions provided in this solicitation.

   b. *Personnel* - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. *Provide resumes for all key staff members,* describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and *provide resumes for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.*

   c. *Resources* - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. *(Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)*

   d. *Other considerations* - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects, etc. Note: If the research plan includes the use of human subjects or animals, refer to paragraphs Sections 4.2.8 and 4.2.9 of this solicitation for further guidance.

   Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

   If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

Resource Sharing Plan(s). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions, etc.), this must be explained in the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

1. *Data Sharing Plan*: Offerors seeking $500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.). See Data-Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/) or http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html.

2. *Sharing Model Organisms*: Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state appropriate reasons why such sharing is restricted or not possible. See Sharing Model Organisms Policy (http://grants.nih.gov/grants/policy/model_organism/index.htm), and NIH Guide NOT-OD-04-042 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

3. *Genome Wide Association Studies (GWAS)*: Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088 (http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and http://gwas.nih.gov/.

e. *Appendices*

(1) **Work Statement** – The Contracting Officer may require the offeror to develop a Statement of Work similar in format to the sample in Appendix E (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf)). Create this from your detailed approach and methodology. It will be incorporated into the final contract document. Do not include proprietary information.

(2) **Commercialization Plan** – Required for the Phase II portion of ALL Fast-Track proposals.

The Phase II portion of Fast-Track proposals must include a succinct Commercialization Plan. The Commercialization Plan is limited to *12 pages*. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, “Commercialization Plan,” and provide a description in each of the following areas:

a. ***Value of the SBIR Project, Expected Outcomes, and Impact.*** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.

b. ***Company.*** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will

meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

c. ***Market, Customer, and Competition.*** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.

Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. (*It is very important that you understand and know the competition*.)

d. ***Intellectual Property (IP) Protection.*** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.

e. ***Finance Plan.*** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:

- Letter of commitment of funding.
- Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
- Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
- Specific steps you are going to take to secure Phase III funding.

f. ***Production and Marketing Plan.*** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.

g. ***Revenue Stream.*** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are *encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization* of the product(s) or service(s) resulting from the SBIR contract.

Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or “angels”; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

6. **Summary of Related Activities** - Use Appendix F (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)).

7. **Number of Copies** - Submit an original and 9 copies.

6.3 BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)).
2. **Proposed Cost Breakdown – For Phase I**, use Appendix C (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project. **For Phase II Fast-Track**, use Appendix C. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.
3. **NIH Policy on Threshold for Negotiation of Facilities and Administrative (F&A)/Indirect Costs (IDC) Rates for SBIR proposals** - SBIR offerors who propose in the contract an F&A/IDC rate of 40 percent of total direct costs or less will not be required to provide further justification at the time of award, and F&A/ID costs will be awarded at the requested rate. However, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for F&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) should be used when calculating proposed F&A/ID costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

   SBCs are reminded that only actual F&A/ID costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual F&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS. DFAS will negotiate F&A/IDC rates for SBCs receiving awards if the requested rate is greater than 40 percent of total direct costs.
4. **Number of Copies** - Submit an original and 4 copies.

7. METHOD OF SELECTION AND EVALUATION CRITERIA

All Phase I and Fast-Track proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria in Section 7.1, a panel of scientists, consisting primarily of nongovernment experts knowledgeable in the disciplines or fields under review, will evaluate proposals to determine the most promising technical and scientific approaches. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposal or any specific number of proposals in a given topic. It also may elect to fund several or none of the proposed approaches to the same topic or subtopic.

7.1 EVALUATION PROCESS

Your proposal will be peer reviewed by a panel of scientists selected for their competence in relevant scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. When relevant, reviewers will be instructed to comment on the reasonableness of the following Resource Sharing Plans, or the rationale for not sharing the following types of resources. However, reviewers will not factor the proposed resource sharing plan(s) into the determination of scientific merit or priority score. Program staff within the funding organization will be responsible for monitoring the data sharing policy

- Data Sharing Plan [http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]
- Sharing Model Organisms [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html]
- Genome Wide Association Studies (GWAS) [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html].

The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals recommended for award, may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject

research issues. The Institute program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component and commercial potential. A Phase I or Fast-Track contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all acceptable proposals is not guaranteed.*

7.2 TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. (Preliminary data are not required for Phase I proposals.)	40%
2. The qualifications of the proposed PDs/PIs, supporting staff, and consultants. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application. The commercial potential of a proposal will be assessed using the following criteria: a. Whether the outcome of the proposed research activity will likely lead to a marketable product or process. b. The offeror's discussion of the potential barriers to entry and the competitive market landscape.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS (FOR FAST-TRACK ONLY)	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II.	30%
2. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by (a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects, (b) commitments of additional investment during Phase II and Phase III from private sector or other non-SBIR funding sources, and (c) any other indicators of commercial potential for the proposed research.	30%

FACTORS FOR PHASE II PROPOSALS (FOR FAST-TRACK ONLY)	WEIGHT
3. The qualifications of the proposed PDs/PIs, supporting staff and consultants. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	25%
4. The adequacy and suitability of the facilities and research environment.	15%

7.3 PROPOSAL DEBRIEFING

Offerors will be notified promptly in writing if their proposals are no longer being considered for award. Offerors may request a debriefing by submitting a written request to the Contracting Officer within three days of receipt of the notification. Untimely requests may be accommodated at the Government's discretion.

7.4 AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

8. CONSIDERATIONS

8.1 AWARDS

1. The award instrument will be a contract.
2. A profit or fixed fee may be included in the proposal, as specified in Federal Acquisition Regulation (FAR) Part 15.404-4. The fee will be negotiated as an element of the potential total contract amount over and above allowable costs.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. Normally, Phase I contracts may not exceed $150,000. Phase II contracts normally may not exceed $1,000,000—including direct costs, indirect costs, and negotiated fixed fee.
5. Cost-sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an evaluation factor in the consideration of your proposal. Cost-sharing is an explicit arrangement under which the contractor bears some of the burden of reasonable, allocable, and allowable contract cost. If cost-sharing is proposed, it should be reflected in your budget summary.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS	NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH) National Cancer Institute (NCI)	37	Scientific and Technical Merit Review: March-May 2012 Anticipated Award Date: August-September 2012
National Institutes of Health (NIH) National Center for Research Resources (NCRR)	1-2	Scientific and Technical Merit Review: February 2012 Anticipated Award Date: July 2012
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	18-29	Scientific and Technical Merit Review: February-April 2012 Anticipated Award Date: July-September 2012
National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA)	2-4	Scientific and Technical Merit Review: March 2012 Anticipated Award Date: July-August 2012
National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	1	Scientific and Technical Merit Review: March-May 2012 Anticipated Award Date: August-September 2012
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	15-21	Scientific and Technical Merit Review: March 2012 Anticipated Award Date: August 2012
Centers for Disease Control and Prevention (CDC) Center for Global Health (CGH)	2	Scientific and Technical Merit Review: May-June 2012 Anticipated Award Date: August 2012
Centers for Disease Control and Prevention (CDC) National Center for Birth Defects and Developmental Disabilities (NCBDDD)	1	Scientific and Technical Merit Review: May-June 2012 Anticipated Award Date: August 2012
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	2	Scientific and Technical Merit Review: May-June 2012 Anticipated Award Date: August 2012

AWARDING COMPONENTS	NO. OF AWARDS	ESTIMATED TIME OF AWARD
Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	3	Scientific and Technical Merit Review: May-June 2012 Anticipated Award Date: August 2012
Centers for Disease Control and Prevention (CDC) Office of Public Health Preparedness and Emergency Response (OPHPR)	1	Scientific and Technical Merit Review: May-June 2012 Anticipated Award Date: August 2012

8.2 MONTHLY PROGRESS REPORT

Contractors will be required to submit monthly progress reports during Phase I along with their invoices. Phase II reports will be required at intervals stipulated in the terms and conditions of award.

8.3 FINAL REPORT

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project objectives, the activities that were carried out, and the results obtained. **An original and two copies** of this report must be submitted as directed by the Contracting Officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports must be submitted as specified in the contract or as directed by the Contracting Officer.*

8.4 PAYMENT

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the Central Contractor Registration (CCR) database before the award of a contract. The registration site for the CCR is http://www.ccr.gov.

Payments on Phase I contracts may be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

8.5 LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government, however, may retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (DHHS) recognizes that, in responding to this solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which

such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the DHHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The DHHS may not be able to withhold data that has been requested pursuant to the FOIA, and the DHHS FOI officials must make that determination. The Government is not liable for disclosure if the DHHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for Government purposes only.

(1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the Small Business Concern (SBC), or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.

(2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) unless, subject to paragraph (3)of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR offeror. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

(3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR program, as described in Section 4 of the SBIR Policy Directive, dated September 24, 2002. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only: (i) Upon expiration of the protection period applicable to the SBIR award, or (ii) by agreement between the awardee and the agency.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that: "This publication was made possible by contract number _____ from (DHHS awarding component)" or "The project described was supported by contract number _____ from (DHHS awarding component)."

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in

certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of a patent application.

Inquiries or information about additional requirements imposed by 37 CFR 401 should be obtained from local counsel or from:

Office of Policy for Extramural
Research Administration,
Division of Extramural Inventions and
Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Drive, MSC 7980
Bethesda, MD 20892-7980
Phone: (301) 435-0679
Fax: (301) 480-0272
E-mail: jpkim@nih.gov

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 U.S.C. 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

Awardees are encouraged to submit reports electronically using Interagency Edison (http://www.iedison.gov). Information from these reports is retained by the NIH as confidential and submission does not constitute any public disclosure. Failure to report as described at 37 CFR Section 401.14 is a violation of 35 U.S.C. 202 and may result in loss of the rights of the recipient organization. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via e-mail at Edison@od.nih.gov.

Resource Sharing Plan(s). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value of, and advance research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions, etc.), this must be explained in the Resource Sharing section of the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

(a) Data Sharing Plan: Investigators seeking $500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.) Offerors are encouraged to discuss data-sharing plans with their program contact. See Data-Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/) or http://grants.nih.gov/grants/guide/ notice-files/NOT-OD-03-032.html.

(b) Sharing Model Organisms: Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms and related resources, or state appropriate reasons why such sharing is restricted or not

possible. See Sharing Model Organisms Policy (http://grants.nih.gov/grants/policy/model_organism/index.htm), and NIH Guide NOT-OD-04-042 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

(c) Genome Wide Association Studies (GWAS): Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or provide an appropriate explanation why submission to the repository is not possible. A genome-wide association study is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088 (http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and http://gwas.nih.gov/.

Royalties. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

1. Name and address of licensor.
2. Date of license agreement.
3. Patent numbers.
4. Patent application serial numbers, or other basis on which the royalty is payable.
5. Brief description (including any part or model number of each contract item or component on which the royalty is payable).
6. Percentage or dollar rate of royalty per unit.
7. Unit price of contract item.
8. Number of units.
9. Total dollar amount of royalties.
10. If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

8.6 PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

For Phase I projects, small business concerns must perform a minimum of two-thirds or 67% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

For Phase II projects, small business concerns must perform a minimum of one-half or 50% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

The Contracting Officer must approve deviations from these requirements in writing after consultation with the agency SBIR Program Manager/Coordinator.

Contractor Commitments. Upon award of a contract, the contractor shall be required to make legal commitments through acceptance of Government contract clauses in the Phase I contract. The outline that follows is illustrative of the types of provisions required by the Federal Acquisition Regulations that shall be included in the Phase I contract. This is not a complete list of provisions to be included in Phase I contracts, nor does it contain specific wording of these clauses. Copies of complete terms and conditions applicable to your contract are available upon request.

1. ***Standards of Work.*** Work performed under the contract must conform to high professional standards.
2. ***Inspection.*** Work performed under the contract is subject to Government inspection and evaluation at all times.

3. ***Termination for Convenience.*** The Government may terminate the contract at any time for convenience if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
4. ***Disputes.*** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. ***Equal Opportunity.*** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. ***Affirmative Action for Veterans.*** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. ***Affirmative Action for Handicapped.*** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. ***Gratuities.*** The Government may terminate the contract if any gratuities have been offered to any representative of the Government to secure the contract.
9. ***American-made Equipment and Products.*** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.
10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. ***Default.*** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.
12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).
13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.
14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

8.7 ELECTRONIC AND INFORMATION TECHNOLOGY (SECTION 508)

a. Pursuant to Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794d), as amended by the Workforce Investment Act of 1998, all electronic and information technology (EIT) products and services developed, acquired, maintained, or used under the resultant contract must comply with the "Electronic and Information Technology Accessibility Provisions" set forth by the Architectural and Transportation Barriers Compliance Board (also referred to as the "Access Board") in 36 CFR part 1194. Information about Section 508 provisions is available at http://www.section508.gov/. The complete text of Section 508 Final provisions can be accessed at http://www.access-board.gov/sec508/provisions.htm.

b. The contractor shall submit electronic reports/documents that meet the requirements of Section 508 of the Rehabilitation Act of 1973, as amended by the Workforce Investment Act of 1998. Conformance shall be verified by producing electronic reports/documents that satisfy the HHS Section 508 Checklists and Standards. (See HHS Section 508 Checklists and Standards.) For further guidance, please see http://www.hhs.gov/web/508/index.html.

8.8 ADDITIONAL INFORMATION

1. This solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.
2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.

3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.
4. This solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.
5. The SBIR contract program is not intended as a mechanism to invite unsolicited proposals. Unsolicited SBIR contract proposals shall not be accepted under the SBIR program in either Phase I, Phase II, or Fast-Track.
6. If an award is made pursuant to a proposal submitted in response to this SBIR solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.
7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet at 1-866-705-5711 or via the Internet at https://eupdate.dnb.com/requestoptions/government/ccrreg/. The contractor must also be registered in the Central Contractor Registry (CCR) prior to award of a contract. Registration can be made via the Internet at http://www.ccr.gov.

9. INSTRUCTIONS FOR PROPOSAL SUBMISSION

9.1 RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this solicitation is:
5:00 p.m., Eastern Time
Monday, November 7, 2011

Any proposal, modification or revision received at the offices designated below after the exact time specified for receipt is “late” and will not be considered unless it is received before award is made, and

1. There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government’s control prior to the time set for receipt of offers; or
2. It is the only proposal received.

Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

Proposals may be withdrawn by written notice received at any time before award. Notwithstanding above, a proposal received after the date and time specified for receipt may be considered if it offers significant cost or technical advantages to the Government and it was received before proposals were distributed for evaluation, or within 5 calendar days after the exact time specified for receipt, whichever is earlier.

Note: Modifications or revisions to proposals that result in the proposal exceeding the stated page limitations will not be considered.

9.2 NUMBER OF COPIES

For Phase I, submit the original and 5 copies of each proposal. The Principal Investigator and a corporate official authorized to bind the offeror must sign the original. The 5 copies of the proposal may be photocopies of the original.

For Fast-Track Phase II, submit the original and 9 copies.

For Phase I and Fast-Track Phase II business proposals, submit an original and 5 copies.

In addition to the paper submissions, proposers are also encouraged to submit two CD-Rom's containing a PDF (Adobe Acrobat) copy of the entire proposal (Technical and Business). This does not replace the paper copies but is in addition to them. The paper copy is the official copy for recording timely receipt of proposals. By signing the proposal, the offeror certifies that, as part of the offer, the information in the paper copy is exactly the same as that which is contained on the electronic media.

9.3 BINDING AND PACKAGING OF PROPOSAL

Send all copies of a proposal in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

10. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

Any small business concern that intends to submit an SBIR contract proposal under this solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, e-mail, and topic number(s). If a topic is modified or canceled before this solicitation closes, only those companies that have expressed such intent will be notified.

10.1 NATIONAL INSTITUTES OF HEALTH (NIH)

National Cancer Institute (NCI)

Ms. Anita Hughes
Phone: (301) 435-3805
Fax: (301) 480-0309
E-mail: anita.hughes@nih.gov

Proposals to the NCI, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Anita Hughes
Contract Specialist
Office of Acquisitions
National Cancer Institute
6120 Executive Blvd., EPS, Room 6038
Bethesda, MD 20892-7193 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI*.

National Center for Research Resources (NCRR)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3430
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NCRR, if mailed through the U.S. Postal Service, must be addressed as follows:

Office of Review
National Center for Research Resources
National Institutes of Health, DHHS
6701 Democracy Bl, Room 1072
Bethesda, MD 20892-4874 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NCRR.*

National Heart, Lung, and Blood Institute (NHLBI)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3338
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NHLBI, if mailed through the U.S. Postal Service, must be addressed as follows:

Review Branch
Division of Extramural Research Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7195
6701 Rockledge Drive, MSC 7924
Bethesda, MD 20892-7924 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NHLBI.*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Mr. Matthew Packard
Phone: (301) 443-3041
Fax: (301) 443-3891
E-mail: packardm@mail.nih.gov

Proposals to the NIAAA must be mailed or delivered to:

Mr. Matthew Packard
Chief, NIAAA Contracts Management Branch
NICHD Office of Acquisitions, NIH
5635 Fishers Lane, Room 3019
Bethesda, MD 20892-9304 *

**Change the city to Rockville, MD and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIAAA.*

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Ms. Anita Hughes
Phone: (301) 435-3805
Fax: (301) 480-0309
E-mail: anita.hughes@nih.gov

Proposals to the NIDDK, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Anita Hughes
Contract Specialist
Office of Acquisitions

National Cancer Institute
6120 Executive Blvd., EPS, Room 6038
Bethesda, MD 20892-7193 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDDK*.

National Institute on Drug Abuse (NIDA)

Mr. Brian O'Laughlin
Phone: (301) 443-6677
Fax: (301) 443-7595
E-mail: bo50d@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Mr. Brian O'Laughlin
NIDA R&D Contracts Management Branch
Neurosciences Office of Acquisition
6001 Executive Boulevard
Room 4211, MSC 9559
Bethesda, MD 20892-8402 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDA*.

10.2 CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Office of the Director, Office of the Associate Director for Science

Juliana Cyril, Ph.D., M.P.H.
Deputy Director, Office of Science Quality
Office of the Associate Director for Science
Phone: (404) 639-4639
Fax: (404) 639-4903
E-mail: JCyril@cdc.gov

Center for Global Health (GCH)

Carlos Smiley
Contracting Officer
Phone: (770) 488-1517
Fax: (770) 488-2688
E-mail: CSmiley1@cdc.gov

Proposals to CGH must be mailed or delivered to:

Carlos Smiley
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

National Center for Birth Defects and Developmental Disabilities (NCBDDD)

Theresa Routh-Murphy
Contracting Officer
Phone: (770) 488-2713
Fax: (770) 488-2778
E-mail: TNR3@cdc.gov

Proposals to the NCCDPHP must be mailed or delivered to:

Theresa Routh-Murphy
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

Charlene Allison
Contracting Officer
Phone: (770) 488.2841
Fax: (770).488.4088
E-mail: CAllison@cdc.gov

Proposals to NCEZID must be mailed or delivered to:

Charlene Allison
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

Julio Lopez
Contracting Officer
Phone: (770) 488-2892
Fax: (770) 488-2868
E-mail: jlopez3@cdc.gov

Proposals to NCHHSTP must be mailed or delivered to:

Julio Lopez
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

Office of Public Health Preparedness and Response (OPHPR)

Vivian Hubbs
Contracting Officer, Lead
Phone: (770) 488-2647
Fax: (770) 488-2670
E-mail: VHubbs@cdc.gov

Lawrence McCoy

Contracting Officer
Phone: (770) 488-2087
Fax: (770) 488-2671
E-mail: LMcCoy1@cdc.gov

Proposals to OPHPR must be mailed or delivered to:

Lawrence McCoy
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

11. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit http://nnlm.gov/ or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service
1-800-553-6847
http://www.ntis.gov

National Technology Transfer Center
Wheeling Jesuit College
1-800-678-6882
http://www.nttc.edu/

12. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, treatment, rehabilitation from cancer, and the continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread applications, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management.

It is strongly suggested that potential offerors do not exceed the total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

Phase II proposals may only be submitted upon the request of the NCI Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section 5). Unless the Fast-Track option is specifically allowed as stated within the topic areas below, applicants are requested to submit only Phase I proposals in response to this solicitation.

NCI Phase II Bridge Award

The National Cancer Institute would like to provide notice of a recent funding opportunity entitled the SBIR Phase II Bridge Award. This notice is for informational purposes only and is not a call for Phase II Bridge Award proposals. This informational notice does not commit the government to making such awards to contract awardees.

Successful transition of SBIR research and technology development into the commercial marketplace is difficult, and SBIR Phase II awardees often encounter significant challenges in navigating the regulatory approval process, raising capital, licensure and production, as they try to advance their projects towards commercialization. The NCI views the SBIR program as a long term effort; thus, in order to help address these difficult issues, the NCI has developed the SBIR Phase IIB Bridge Award under the grants mechanism. The previously-offered Phase IIB Bridge Award was designed to provide additional funding of up to $3M and up to three additional years to assist promising small business concerns with the challenges of commercialization. The specific requirements for the previously-offered Phase IIB Bridge Award can be reviewed in the full RFA announcement (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-11-002.html).

The NCI expanded the Phase IIB Bridge Award program in FY2011 to allow previous SBIR Phase II contract awardees to compete for SBIR Phase IIB Bridge Awards. Pending its planned continuation, it is anticipated that the Phase IIB Bridge Award program will be open to contractors that successfully complete a Phase I award as a result of this solicitation, and who are subsequently awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). Provided it is available in the future, NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase IIB Bridge Award under a future Phase IIB Bridge Award grant/cooperative agreement funding opportunity announcement (FOA), if they meet the eligibility requirements detailed therein. Selection decisions for a Phase IIB Bridge Award will be based both on scientific/technical merit as well as business/commercialization potential.

NCI SBIR Technology Transfer

The NCI SBIR Technology Transfer program pilot began in FY 2011 through the solicitation of two topics as part of PHS-2011, Solicitation for SBIR Contract Proposals. This program is continuing in FY 2012 through the inclusion of the two NIH NCI Technology Transfer topics in this solicitation (Topic 310 and Topic 311). Additionally, NIDDK is soliciting one Technology Transfer topic (Topic 075) as part of this program. The Technology Transfer program is modeled after an effort launched by the National Institute of Standards and Technology (NIST) that has successfully demonstrated that this program can help move federal research inventions toward the marketplace. The two NIH NCI Technology Transfer topics included in this solicitation are based on employee invention reports (EIRs) from NCI intramural employees, and are backed by patent applications submitted by the NCI Technology Transfer Center (TTC). The goal of each SBIR-TT topic is to identify a small business which can work under research and commercialization licenses, with SBIR funding, to perform the necessary R&D to advance the technology towards commercialization. Please refer to the project goals of each individual topic (Topic 310, Topic 311, and Topic 075) for additional information on these topics including pre-submission webinars, licensing information, and information on the role of and level of interaction with the inventor. To find out the date of each webinar, please visit (http://sbir.cancer.gov/news/upcoming/).

NCI Topics:

This solicitation invites Phase I (and in certain topics Fast-Track) proposals in the following areas:

255 Development of Anticancer Agents

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 10

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The short term goal of this SBIR contract topic is to support small businesses that are developing novel candidate therapeutic agents of interest. The scope of work may include structure activity relationships (SAR), medicinal chemistry and formulation, animal efficacy testing, pharmacokinetic, pharmacodynamic, and toxicological studies, as well as production of GMP bulk drug and clinical product. These data will establish the rationale for continued development of the experimental therapeutic agent to the point of filing an investigational new drug application (IND) (http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm). Successful projects may be eligible for further development at NCI, through participation in the NCI Experimental Therapeutics (NExT) Program (http://next.cancer.gov/). For this, companies should submit proposals for the development of agents that are in mid to late pre-clinical development (expected time to clinic 1-3 years). The development plan, targeted to oncologic indications, will be reviewed by NCI. Agents for rare cancers are of particular interest to the NCI.

Project goals:

The goal of the NCI SBIR program is to accelerate the development of products that benefit cancer patients. The long term goal of this contract is to enable a small business to bring a fully developed cancer therapeutic agent to the clinic and eventually to the market.

Phase I Activities and Expected Deliverables:

- Specific activities will range from SAR and medicinal chemistry to animal toxicology and pharmacology, depending on the agent selected for development.
- Development plan that details the experiments necessary to file an IND or an exploratory IND.
- Demonstrate ability to deliver results for the initial set of experiments (project-specific, according to the development plan above).

Phase II Activities and Expected Deliverables:

- Complete all experiments (e.g. pharmacokinetics, preclinical efficacy, GMP manufacturing) according to the development plan (can be re-evaluated if needed).
- If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agent in question (oncologic indications).
- Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial (according to FDA's Exploratory IND guidance) (http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/). For additional guidance refer to the following guidance. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf).

277 Development of Companion Diagnostics

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 4

Budget (total costs): Phase I: $200,000 for 9 months; Phase II $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Recently, the demand for companion diagnostics has greatly increased with the recognition that matching the right patient to the right drug can improve patient care and may decrease health care costs. More than a dozen companion diagnostic tests have been approved by the FDA to guide the prescription of products in oncology, cardiovascular disease, and infectious disease. Among them, tests of Philadelphia chromosome, tumor-associated EGFR overexpression, and HER2 protein overexpression have been identified by the FDA as "required" for the identification of candidate cancer patients for receiving Gleevec, Erbitux (cetuximab) and Herceptin (trastuzumab), respectively, in certain indications.

Despite initial success, many therapies in the cancer arena are still lacking prediction and guidance from companion diagnostics. This is true for both primary as well as adjuvant treatments. In particular, many patients die from recurrence and metastasis as a result of unpredicted resistance to drugs and/or radiation developed during therapy, or due to pre-existing tumor insensitivity to the drugs and/or radiation therapy. Guidance towards effective and safe therapy is therefore much in need. Companion diagnostics include tests that are developed after a drug has come to market, tests that are being developed in conjunction with the development of a drug and tests to predict the interaction of novel agents with existing standard of care therapies such as radiation or cytotoxic chemotherapy. This contract topic seeks to stimulate research, development, and commercialization of innovative tests and technology platforms for all these types of companion diagnostic applications. Companies with advanced biomarkers are particularly encouraged to apply.

Project Goals:

The goal of this contract topic is to develop companion diagnostics for selecting patients for which a particular therapeutic regimen, including existing drugs and those in clinical development and radiation, will be safe and effective. Although the example companion diagnostic tests mentioned above are for targeted therapies, tests may also encompass therapeutics outside of this class. These tests include, but are not limited to tumor RNA/protein expression or overexpression, gene mutation or deletion/insertion, allelic variation, and enzymatic deficiency. Noninvasive and minimally invasive sampling methods (e.g., body fluids and mouth swab) are preferred. Other sampling methods are also acceptable if they provide significantly improved predictive value, accuracy, and clinical applicability. This topic is not intended to support the development of assays unless they provide predictive/prognostic information for a therapy. For example, development of an assay for the sole purpose of measuring whether the drug hits its target would not be considered responsive.

Phase I Activities and Expected Deliverables:

- Develop a working test.
- Characterize the variation, reproducibility and accuracy of the test.
- Demonstrate suitability of the test for use in the clinic, conduct benchmarking studies against current tests (if available). Algorithms must be tested with datasets other than those used for their development.
- In cases where the drug for which the companion diagnostics being developed is not yet commercially available on the market, the applicant must provide proof of collaboration or partnership with a large diagnostic company (e.g. Quest, Qiagen) or the entity that is developing the therapeutic agent.
- Deliver the SOP of the working test to NCI for evaluation.

Phase II Activities and Expected Deliverables:

- Demonstrate clinical utility and value by testing sufficient numbers of patients to unequivocally prove statistical significance with regards to patient selection for the therapy.
- If the phase I conclusions are mainly based on animal experiment or *ex vivo* modeling, then a correlation study between these models and treatment in human subjects may be expected.

- Establish marketing partner or alliance with pharmaceutical companies that are developing the therapy unless the therapy is already on the open market.
- Deliver the final SOP to NCI for evaluation.

291 Development of Radiation Modulators For Use During Radiotherapy

(Fast-track proposals will be accepted)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Radiotherapy is employed in the treatment of over half of all cancer patients. Many of those patients however, may suffer some adverse effects from this therapy during and/or after treatment. In addition, in approximately half of the patients treated with curative intent, the tumors recur. Enhancing specific tumor killing and minimizing normal tissue damage from radiotherapy would improve tumor control and patient quality of life. An ideal intervention would enhance both radiation effects in tumors and protect the normal tissues.

Radiosensitizers are agents that are intended to enhance tumor cell killing while having a minimal effect on normal tissues. Recently, two new radiation sensitization drugs have proven clinically effective: Temozolomide treatment with radiotherapy for glioblastoma and Cetuximab treatment combined with radiation for head and neck squamous cell cancers. A large number of other targeted therapies are possible and although some are currently in varying phases of development, there is significant potential for further development of novel agents.

Conventionally*, radioprotectors* are defined as agents given before radiation exposure to prevent or reduce damage to normal tissues, while *mitigators* refer to those agents given during or after a patient's prescribed course of radiation therapy to prevent or reduce imminent damage to normal tissues. Both radioprotectors and mitigators are also being developed as potential countermeasures against radiological terrorism and several have shown promise in pre-clinical testing. In order for these to be developed and useful in clinical radiation therapy applications it is imperative to demonstrate that they do not protect cancer cells.

The importance of developing agents that sensitize tumor cells, protect or mitigate radiation-induced damage in normal tissue, improve survival, quality of life, and palliative care in cancer patients was emphasized in a recent NCI workshop on Advanced Radiation Therapeutics - Radiation Injury Mitigation held on January 25th 2010 (2), and in a workshop on Radiation Resistance in Cancer Therapy: Its Molecular Bases and Role of the Microenvironment on its Expression held Sept 1-3, 2010. Prior workshops have dealt with sensitization, protection, or radiation effects assessment (3,4).

This contract topic aims to encourage the development of innovative and promising radioprotectants, mitigators, or sensitizers that either selectively protect normal tissues (but not tumors) against ionizing radiation or selectively sensitize tumors, thereby increasing the therapeutic ratio of radiation. Proposals for radiation modulators are solicited that include preclinical and/or early phase clinical studies demonstrating safety, efficacy, dose, schedule, pharmacokinetics (PK), pharmacodynamics (PD), and metabolism. Proposals should also demonstrate a clear understanding of regulatory requirements, and should include a regulatory plan including key steps such as a pre-IND meeting with FDA, submitting an investigational new drug (IND) application, approval of clinical trial design, and ultimately drug registration.

Project goals:

The goal is to stimulate collaborations among academic institutions, small businesses, and contract research organizations in order to promote the rapid development of innovative radioresponse modifiers that will decrease

normal tissue injury and/or enhance tumor killing thereby improving radiotherapy outcomes. The long-term goal is to enable small businesses to fully develop, license, and/or market radioresponse modifiers for clinical use.

The contract proposal must describe:

Phase I:

- A quantitative estimate of the patient population that will benefit from the availability of such radioresponse modifiers.
- A plan for generating evidence that the proposed compound(s) protects at least one relevant normal tissue from radiation-induced injury, and/or sensitizes at least two relevant tumor models.
- Either: 1) A plan for generating evidence that the proposed radioprotector(s)/mitigators(s) do not significantly protect cancer cells, or 2) A plan for generating evidence that the proposed radiosensitizer(s) do not significantly sensitize normal cells and tissues.
- The plans must include the methodologies proposed to evaluate the preferential effects on normal tissues or tumors by the compound(s) *in vivo* (including appropriate biomarkers and endpoints as determined during early interactions with the FDA).
- Determination of the optimum dose and schedule *in vivo* based upon preclinical pharmacodynamic and pharmacokinetic studies.
- Statistical validation of the proposed study endpoints including where appropriate, power calculations and rationale for proposed sample sizes.

Phase II:

- The approach to early-phase human trials, as indicated, that are designed taking into account the relevant molecular pathways and targets and aim to gather pharmacodynamic and pharmacokinetic data to confirm the compound's observed behavior in animal studies.
- The approach to assessing the safety and efficacy of the compound(s) in early-phase human trials employing, as appropriate, physician-reported endpoints as well as patient-reported outcomes.

Activities and Expected Deliverables:

Phase I may include primarily preclinical studies. Phase II or "Fast-Track" proposals must contain a section entitled "Regulatory Plan" detailing plans for early involvement of the FDA. There should be a description of how the applicant plans on meeting the requirements to: 1) define suitable biomarkers and endpoints, 2) file IND and 3) design and perform phase 0-2 clinical trials in preparation for product transition to phase 3 clinical trials by groups such as the RTOG. Where cooperation of other partners is critical for implementation of the proposed methodology, the applicant should provide evidence of such cooperation (through partnering arrangement, letters of support, etc.).

The following deliverables may be required depending on a compound's maturity in the developmental pipeline:

Phase I:

- Selection and approval of cell panels for *in vitro* testing.
- Demonstration of drug solubility and uptake using cultured normal and transformed cells.
- Study design for determining clonogenic survival or approved alternative tailored to the mechanism of each tested compound.

- Clonogenic survival data or approved alternative validating lack of drug toxicity in normal cells, efficacy and specificity of radioprotection for normal cells and/or efficacy and specificity of radiosensitization for tumor cells.
- Preliminary evidence for lack of toxicity to normal tissue and/or lack of acute toxicities such as vomiting, hypotension etc , preferably demonstrated *in vivo*.
- Documentation providing a top-level description of the protocols and the testing results should be provided to NCI as part of the Phase I progress report.

Phase II:

For advanced pre-clinical work:

- Design of an NCI/institutional animal care and use committee approval of *in vivo* experimentation plan including statistical validation of experimental design/sample size including power calculations. In addition, selection and approval of tumor cell panel and normal tissues for *in vitro* testing.
- Demonstration of bioavailability PK and PD in rodent model.
- For radiation protectors / mitigators: demonstration by physiologic testing and histological assessment that irradiated normal tissues are spared over a 6-month period.
- Demonstration of effects (sensitization or lack of protection as appropriate) on tumors using *in vivo* radiation regrowth delay assays.
- Collection of data validating lack of drug toxicity, efficacy, and specificity for normal cells over tumor cells in the case of radiation protectors/mitigators.

For proposals advancing to early phase human trials:

- Identify GMP drug source
- Obtain IND approval
- Provide evidence of established clinical collaboration
- Submitted protocol for IRB approval
- Define suitable clinical endpoints and patient-oriented outcomes.

Documentation of the testing protocol and testing results should be provided to NCI as part of the Phase II progress report for pre-clinical studies.

300 Reformulation of Cancer Therapeutics using Nanotechnology

(Fast-track proposals will be accepted.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The design of novel therapies and drug delivery systems for cancer is being enabled by nanotechnology. Nanoscale devices carrying therapeutic payloads and delivered within close proximity of the tumor *in vivo* will play

a significant role in increasing the effectiveness of the treatment while decreasing severity of side effects. Such techniques would be highly relevant, particularly for organs that are difficult to access because of a variety of biological barriers, including those developed by tumors. The successful delivery of well established chemotherapeutics using nanoparticle-based delivery platforms has previously been demonstrated; however, an even bigger opportunity that can be enabled by nanoparticle delivery is the potential to mitigate the adverse properties of once promising drugs which failed to reach clinical trials or failed in clinical trials due to excessive toxicity and can be reformulated into safe and viable therapies using nanoparticles. Furthermore, poor oral bioavailability, poor solubility in biological fluids, inappropriate pharmacokinetics, and lack of efficacy within a tolerable dose range can be also addressed using such reformulation approaches.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based platforms for the reformulation of cancer therapeutics.

Project Goals:

The goal of this project is to identify and evaluate the potential of candidate nanotechnologies to significantly improve the performance of anti-cancer agents. Specifically, this topic is intended to fund nanotechnology delivery systems which will enable anti-cancer drugs which could not otherwise be delivered in free form due to their excessive toxicity, poor oral bioavailability, poor solubility in biological fluids, inappropriate pharmacokinetics, and lack of efficacy within a tolerable dose range to be re-examined as potential therapies for cancer treatment. Drug-nanoparticle constructs must yield a significant improvement in properties with respect to the free drug and FDA-approved formulations of the drug. Of special interest are drug-nanoparticle constructs which mitigate the unacceptable properties of the drugs which may not currently be administered to humans in free form.

These drug-nanoparticle constructs can take, for example, the form of multi-functional targeted nanoparticles or multi-chamber chips carrying encapsulated drugs. Further, the drug-nanoparticle constructs may also utilize imaging agents for a combination of therapeutic and diagnostic modalities that aim to provide real-time feedback and monitoring of therapy. They may include, but are not limited to the following:

- novel therapeutic nanodevices
- devices involving novel tumor targeting and concentrations schemes
- novel drug loading and releasing schemes
- novel therapeutic or theranostic nanodevices which are able to cross the blood-brain barrier

Offerors must identify the drug which they intend to reformulate for this topic. Offerors must also cite at least one clinical trial, one paper in a respected journal or submit original data which clearly demonstrates the reason(s) which prevented the drug from receiving FDA approval or entering clinical trials. Offerors must provide evidence that they can synthesize, purchase or otherwise obtain the drug as part of their proposal in order to be eligible for this topic (i.e., Offerors are solely responsible for obtaining the drug). Intellectual property issues and material transfer agreements regarding the usage of the drug are the responsibility of the offerors. **Peptides, proteins and nucleic acids are not acceptable drug candidates for this topic.**

Phase I Activities and Expected Deliverables:

- Proof-of-concept encapsulation or attachment of undeliverable therapeutic agent to nanoparticle
- *In vitro* demonstration of nanoconstruct stability and controlled release of therapeutic agent from nanoconstruct
- Proof-of-concept *in vitro* studies demonstrating efficacy in relevant cell lines
- Proof-of-concept small animal studies demonstrating improved therapeutic efficacy and improved therapeutic index, bioavailability, solubility, and/or pharmacokinetics as compared to the use of free drug (utilizing an appropriate animal model)

Phase II Activities and Expected Deliverables:

- Long Term Toxicity Studies
- Biodistribution Studies
- Initiation of large animal studies
- Demonstration of nanotherapeutic manufacturing and scale-up scheme
- IND-enabling studies carried out in a suitable pre-clinical environment

301 Probing Tumor Microenvironment Using *In Vivo* Nanotechnology-based Sensors

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Biological fluids and tissue biopsies provide important information with respect to a diagnosis of cancer and to efficacy of its treatment. The collection of both (especially the biopsy) is invasive and can be achieved only in single time points with limited frequency. The analysis of biological fluids (blood, urine), which are easier to collect, do not provide for direct representation of the tumor development. It assesses the status of the tumor only on the basis of biomarkers which are given away by the tumor and release to the biological fluid. The release of these biomarkers and its close correlation to tumor growth varies from organ to organ and its kinetics is not well understood.

On the other hand, ability to monitor tumor microenvironment directly *in vivo*, in close proximity to the tumor site, will facilitate for a significant improvement in the collection of data (metabolite concentrations, biomarkers, enzymatic activity) associated with tumor growth and its behavior under treatment. It will also contribute to advancing out understanding of metastasis. Nanotechnology allows for the design and manufacture of complex multi-functional particles and devices which could yield temporal data for these important parameters *in vivo*. This could be achieved in several ways: 1) through the development of nanoparticles with surfaces or biological coatings which recognize parameters associated with tumor microenvironment where tumor-targeted particles are introduced systemically; 2) through the design of implantable biochemical sensors which can collect data over the extended period of time; 3) through the design of circulating nano-sensors which collect data while traveling in blood stream and then are excreted from the body for further evaluation.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based diagnostic platforms capable of monitoring tumor microenvironment *in vivo*.

Project Goals:

The goal of the project is to develop nano-enabled in vivo diagnostic platforms that can provide increased sensitivity and specificity in detecting cancer or cancer metastasis or monitoring effectiveness of the treatment in pre-clinical animal models of cancer and/or in human patients. These capabilities will offer clinicians a way to maximize opportunities for early disease recognition and produce positive clinical outcomes.

Potential relevant sensing nanoplatforms could include, but are not limited to:

Nano-enabled Sensing Platforms for In Vivo Applications

Examples: Several different design modalities can be considered: 1) use of nanoparticles which are introduced systemically or locally and possess surfaces or biological coatings which recognize parameters associated with tumor microenvironment and report their change (through the change of electrical, optical, magnetic signal); 2) use of biochemical sensors which are implanted and can collect data over the extended period of time; 3) use of systemically introduced nanoparticles or nanodevices which collect the data and subsequently are excreted for further evaluation.

Potential Applications: Diagnosis of cancer or cancer metastasis or long-term monitoring of treatment effectiveness based on biochemical markers or CTCs or other physiological indicators such as pH or oxygen level.

Given the diversity of potential applications discussed above, submitted proposals should place emphasis on the specific nanotechnology-enabling component of the proposed platform.

Phase I Activities and Expected Deliverables:

- Design describing:
  - unique *in vivo* sensing capabilities enabled by nanotechnology
  - proof of concept experiments
  - benchmarking experiments against conventional methodologies
- First-stage validation of design in relevant preclinical samples
  - Demonstrate 1) the recognition of relevant clinical biomarkers or other tumor microenvironment indicators by nanoparticles or nanodevices incubated in blood, urine, or other biological fluids *in vitro* at varied concentrations and concentration profiles, and 2) isolation of nanoparticles from the biological fluid
- Successful completion of benchmarking experiments demonstrating a minimum of 5x improvement against conventional methodologies

Phase II Activities and Expected Deliverables:

- Second-stage validation of design for potential clinical adaptation
  - Demonstrate the recognition of relevant clinical biomarkers or other tumor microenvironment indicators by nanoparticles or nanodevices in relevant animals models including large animals
- Systematic study of sensitivity and specificity of the sensor platform in pre-clinical or clinical samples and demonstrate reproducibility
- Collect data from a statistically significant number of animals or patients in preparation for an IDE application
- Submit IDE application to obtain necessary regulatory approval for clinical validation

306 Development of Innovative Algorithms for Processing & Analysis of *In Vivo* Images

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-4

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Image processing algorithms are increasingly important as imaging and image-guided intervention technologies become critical in screening, diagnosis, staging, treatment and monitoring of cancer patients. The use of *in vivo* imaging modalities such as MRI, X-ray, CT, Positron Emission Tomography, Nuclear Medicine, Ultrasound, Optical Coherence Tomography, and Photo-acoustic imaging, as well as multi-modality imaging for the management of cancer patients has continued to increase exponentially. As more and more imaging data becomes available, innovative software algorithms for image processing and analysis will be a critical need for effective use of the information presented by medical images.

Improved image processing and analysis software serves the needs of cancer patients by enhancing the ability to distinguish viable cancer from necrotic cells, or swelling, or other benign causes of persistent radiographic abnormalities. Advanced software also allows the radiologist to detect cancer earlier, when treatments may be more effective, and to perform a non-invasive or image-guided needle biopsy approach to diagnose cancer and avoid an open surgical procedure. In many cases, advanced visualization and post processing algorithms enable faster and more accurate assessment of disease extent to guide treatment options, at the time of diagnosis and during treatment.

Project goals:

The short-term goal of this topic is to develop robust algorithms to enable faster and more accurate decision making for imaging and image-guided interventions. These include but are not limited to the following:

- Algorithms that enable real-time reconstruction and display of images for image-guided interventions.
- Extraction of clinically relevant quantitative information from images.
- Improvements in multimodality image co-registration, image fusion and deformable models for image visualization and image-guided interventions.
- Optimization in image processing techniques that enhance visualization (e.g. segmentation tools, noise reduction etc) and facilitates image analysis.
- Novel methods for feature extraction, object recognition to develop tools for computer-aided detection (CAD) and monitor changes over time.
- Algorithms to process large image data sets quickly.

Development of algorithms for image acquisition and/or routine image processing for a new medical imaging device is not appropriate for this solicitation and should not be submitted. Image processing algorithms that are **vendor independent** and can be applied to **multiple modalities** are strongly encouraged by the NCI. However, this does not exclude the possibility that future commercialization may be executed initially through a single vendor.

It is expected that the proposed innovation will be driven by clinical practice. Therefore, in addition to standard proposal components; the contract proposal must contain specific discussion of the target patient population and evidence of an existing clinical problem which is addressed by the proposed method. The proposal must also contain an analysis of competitive methods to address the same problem and explanation of competitive technical advantages of proposed algorithm. All Phase II or Fast-Track proposals MUST contain a section entitled “Regulatory Plan” that demonstrates an understanding of the regulatory requirements for clearing the software device through the FDA, details the company’s plan to meet the requirements, and explains how the proposed work helps to meet these requirements. If regulatory approval is not expected to be required, the offeror must provide an extensive justification for this.

The long-term goal of the program is to create software packages with novel algorithms that can be integrated into one or more different commercial imaging platforms, where appropriate.

Applicants are encouraged to explore affiliations with the NCI Research Networks such as the Quantitative Imaging Network (QIN) (http://grants.nih.gov/grants/guide/pa-files/PAR-08-225.html) which aims to develop a consensus on methods to validate software and modeling methods , share ideas and approaches to validate and standardize imaging data and related imaging metadata for quantitative measurements of responses to cancer therapies.

Phase I Activities and Expected Deliverables:

- Development of an innovative algorithm to improve image processing methods for imaging or image-guided interventions for cancer patients.
- Preliminary validation of the algorithms in phantoms or clinical patient image data-sets, as appropriate. The NCI Cancer Imaging Program has a link to publically available resources for digital image data-sets: (http://imaging.cancer.gov/programsandresources/InformationSystems/ImageArchiveResources/page14).
- In-person software demonstration to NCI Program staff (travel to NCI must be included in the budget).
- Final progress report should include plans for distribution of the product as part of the commercialization objectives. If co-operation of other companies or large equipment manufacturers is required for commercialization, provide evidence of established communication with potential partners.

Phase II Activities and Expected Deliverables:

- Establishment of an FDA-compliant Quality System for software development.
- Production of a clinic ready software package with user-friendly graphical user interface.
- Extensive clinical validation using reader studies with prospective data to demonstrate improvements from the developed algorithms including usability as compared to current standard of care.
- Draft user manual.
- Provide Standard Operating Procedure for clinic-ready software to NCI.
- Present final results to NCI.

307 Novel Imaging Agents to Expand the Clinical Toolkit for Cancer Diagnosis, Staging, and Treatment

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $250,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Medical imaging plays a key role in clinical management of cancer patients. Cancer imaging agents are used in conjunction with medical imaging equipment, and, by highlighting the contrast between normal and malignant tissues, they allow the collection of information on cancer presence, spread, and metabolism.

Recent scientific advances in nanotechnology, radiochemistry, reporter gene imaging, cancer stem cell imaging, and other fields now enable the development of novel imaging agents for:

- Early detection and diagnosis of cancer
- Differentiation of benign disease from malignancy
- Stratification of patients for the purpose of selecting a cancer therapy
- Surgical planning
- Evaluation of tumor response to chemotherapy and radiation therapy
- Detection of cancer recurrence

However, despite significant preclinical scientific progress, very few cancer imaging agents are actually available in the clinic. Therefore, this SBIR contract topic seeks to stimulate the commercialization of novel imaging agents, including: nanotechnology-based imaging agents, radiopharmaceuticals for positron emission tomography (PET) and single photon emission computed tomography (SPECT), targeted contrast agents for X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), optical contrast agents, and reporter gene imaging technologies.

One specific area of interest under this topic is the development of single-domain antibody fragments used to target radionuclides for imaging and targeted radiotherapy of cancer. Single-domain antibody fragments comprise the single variable region of naturally-occurring antibodies that lack a light chain or engineered antibody fragments. This type of small protein or peptide has advantages over conventional antibodies and antibody fragments in terms of favorable and tunable clearance kinetics, ability to recognize hidden or uncommon epitopes, agent format flexibility, and ease of manufacture. Therefore, developing an imaging technology for early diagnosis of cancer at the molecular level based on single domain antibody fragments will be encouraged.

Project goals:

The short-term goal of this SBIR contract topic is to support research and development activity at small businesses that are developing cancer imaging agents. The imaging agent should be novel and, when appropriate, have high affinity and specificity against tumor targets. It should also display fast *in vivo* clearance, rapid tumor accumulation, sufficient *in vivo* stability and good biovailability, and low immunogenicity and toxicity. The work scope may include animal testing, formulation, GMP production, pharmacokinetic studies, pharmacodynamic studies, and toxicological studies. These data will support the rationale for continued development of the experimental medical imaging agent to the point of filing an Investigational New Drug application (IND).

The long-term goal of this contract topic is to enable small businesses to bring novel classes of fully developed cancer imaging agents to the clinic and the market. Therefore, businesses are encouraged to submit applications for development of lead compounds representing novel technology platforms.

Phase I Activities and Expected Deliverables:

Phase I activities should generate scientific data confirming the clinical potential of the proposed contrast agent. Some of the expected activities are:

- Preparation of an imaging agent.
- Demonstration of capabilities enabled by the imaging agent with a high signal-to-noise ratio.
- Quantification of the imaging signals to determine the agent affinity and specificity.
- Proof of concept pre-clinical studies.
- Preliminary toxicological studies.

- Preparation of a development plan that describes in detail the experiments necessary to file an IND or an exploratory IND.
- Presentation of the Phase I results and the development plan to NCI staff.

The Phase I research plan must contain specific, quantifiable, and testable feasibility milestones.

Phase II Activities and Expected Deliverables:

Phase II should follow the development plan laid out in the Phase I, and should further support commercialization of proposed cancer imaging agents. Some of the expected activities are:

- Completion of all pre-clinical experiments according to the development plan.
- Demonstration of fast *in vivo* clearance, rapid tumor accumulation, sufficient *in vivo* stability, good bioavailability, and low immunogenicity/toxicity.
- Demonstration of high reproducibility and accuracy of the imaging technology in several animal models.
- When appropriate, demonstration of similar or higher specificity and sensitivity of the technology when compared to other imaging technologies.
- When appropriate, demonstration of capabilities to monitor efficacy of drugs in tumor cell lines and/or animals.
- Production of sufficient amount of clinical grade material suitable for an early clinical trial.
- If warranted, filing of an IND or an exploratory IND for the candidate imaging agent.
- Completion of a small-scale clinical study.

The Phase II research plan must contain specific, quantifiable, and testable feasibility milestones.

308 Automated Collection, Storage, Analysis, and Reporting Systems for Dietary Images

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Current dietary assessment methods and systems largely depend on time and resource intensive self-report and/or recall methods. Accuracy of the assessment is often compromised when diet is assessed via self-report because of the cognitive challenges in recalling or reporting quantities, types, and preparation of foods eaten. Dietary assessment methods that do not rely solely on self-report and recall could enhance the accuracy and efficiency of dietary intake data collection and contribute to improved understanding of the diet-disease relationship. Technological and analytic advances over the past decade have led to more objective methods to assess dietary intake. Leading examples include sophisticated dietary image or short video capture devices, that may be housed on a mobile phone platform and paired with speech recognition, text interface, and/or geospatial location. With the advent of electronic medical records and the focus on the epidemic of obesity and related co-morbidities, clinicians, researchers, and practitioners are increasingly interested in using objective measures to monitor patient/participant behavior as a tool for chronic disease prevention or management and health research.

The development of an easily deployable architecture for image-based dietary data transfer, storage, analysis, and reporting will support the potential to increase understanding of the relationship between diet and cancer risk. However, software systems necessary to manage and analyze the rich media collected by mobile sensors are currently limited. The complexity of data management and analysis needed to provide image-based measures of dietary intake presents a significant barrier to the integration of these measures into clinical practice and trials, epidemiological research, and behavioral monitoring applications. To overcome current barriers and facilitate integration of image-based dietary measures into applications including electronic medical records and other health information systems, contracts shall stimulate development of an easily deployable architecture for data collection, transfer, storage, analysis, and reporting of dietary intake.

Project objectives include:

1) Development of a mobile application to facilitate and control the collection and transfer of dietary images or video, and any associated information such as annotations, probes, or geospatial location.

2) Development of a standardized dietary rich media database architecture and procedures to import and store data transferred from the mobile application.

3) Development of transparent and modifiable analytic tools that can incorporate existing and evolving methods to generate individual and group level dietary intake measures from dietary images and associated data.

4) Development of reporting systems to communicate outputs to patients/subjects, electronic medical records, health surveillance systems, or researchers.

Project Goals:

This topic addresses the need to develop high throughput, efficient methods to standardize collection, processing, and reporting of image-based dietary intake measures, for use in clinical and research settings, and for case management in prevention or treatment of chronic disease. This topic's goal is to encourage development of mobile applications to facilitate and control the collection and transfer of dietary rich media files; and paired systems for data importation, storage, analyses, and output reporting of image-based dietary intake measures. Required data elements include dietary images or short video capture of consumed foods. Additional elements may include (but are not limited to) speech recording and recognition, text interface, and/or geospatial location. The NIH Genes, Environment, and Health Initiative (GEI) Exposure Biology Program has supported development of technology and analytic methods for image-based dietary assessment with relevance to the current topic.

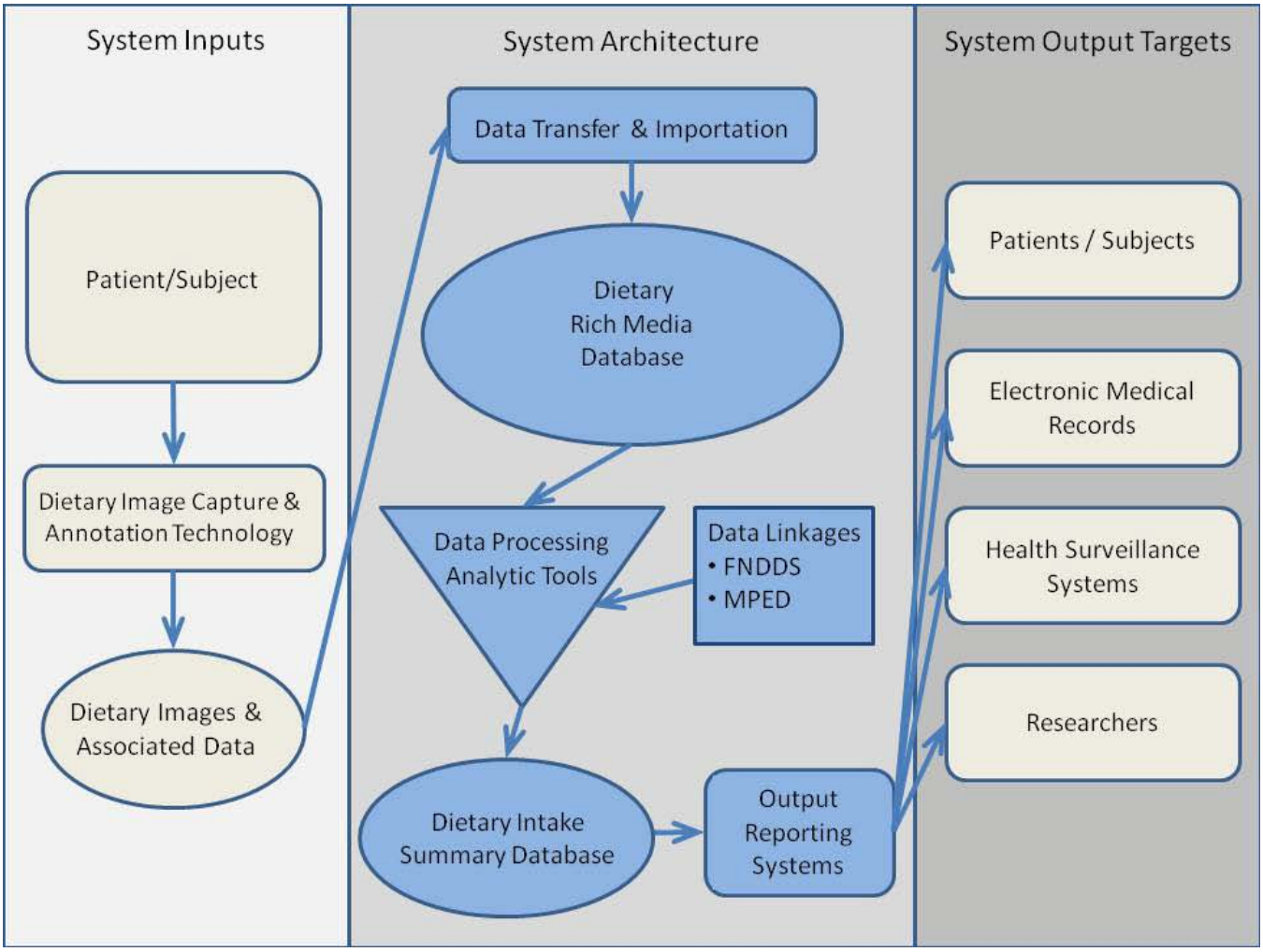
An essential task for each proposal is the application or development of transparent and expandable analytic tools to generate summary individual level dietary measures from collected dietary rich media files. Data processing applications and analytic tools may be drawn from established or emerging methods for dietary image analysis research and practice. An expandable set of analytic tools for processing image and supplemental dietary input data shall be developed, including automated food item identification, quantity estimation, and consumed volume reconstruction based on pre and post-meal images/video. Data processing and analytic tools must provide linkages to established nutrient databases including the USDA Food and Nutrient Database for Dietary Studies (FNDDS) and the USDA MyPyramid Equivalents Database (MPED). Capacity to incorporate or expand to handle additional data is also encouraged, such as Global Positioning System (GPS) location or linkage to the Gladson Nutrition Database which includes Universal Product Code (UPC) data. Data linkages are required within the Dietary Intake Summary Database to identify individual level data characteristics based minimally on eating occasion or meal, day, and week.

Proposals must demonstrate implementation or development of data standards and capacity for sharing dietary summary measures via output reporting systems. Recommended short term targets for dietary outputs include ability to provide reports to patients/participants, health systems, and researchers; with longer term targets to provide reports directly to electronic medical records and public health surveillance systems. Recommended reports are consistent with current health outcomes policy priorities and objectives in the Meaningful Use Matrix for electronic health records established by the Health Information Technology Policy Committee (see http://healthit.hhs.gov/portal/server.pt).

Figure 1 summarizes data flow through the system architecture. Potential steps within a developed systems data cycle are described below:

1) A front end mobile application to facilitate and control dietary rich media data collection and transfers is deployed to a user's smartphone.
2) Using the front end mobile application, a user collects dietary image or short video files and system specific annotation options (such as speech recognition, text interface, or probing options) and/or geospatial location.
3) The front end mobile application wirelessly transfers the collected data to the backend system for data management and processing.
4) Using automated procedures, the transferred data is screened and imported into the structured Dietary Rich Media Database.
5) Automated analytic tools are used to process images and supplemental data for food item identification, quantity estimation, and consumed volume reconstruction based on pre and post-meal images/video.
6) Analytic tools link to established nutrient databases including FNDDS and MPED for nutrient intake and equivalents estimation.
7) Food and nutrient intake summary measures are stored within a Dietary Intake Summary Database with linkages allowing individual or group outputs based on eating occasion or meal, day, week, and/or other periods of assessment.
8) Reporting systems provide outputs directly to information users, such as the patient, research study site, or the patient's electronic medical records for review and follow-up by health care team members.

Figure 1. Schematic of data cycle architecture to enable image-based dietary data collection, transfer, storage, analysis, and reporting in clinical and research applications



Phase I Activities and Expected Deliverables:

- Establish a project team including expertise in dietary assessment and food and nutrition science, image-based technologies for dietary assessment, advanced image data/signals processing methods, and database and computational systems that will effectively address all objectives of the current topic.
- Provide a report including detailed description and/or technical documentation of the proposed:
  - Database structure for the Dietary Rich Media Database
  - Data standards for collection, transfer, importation, and storage of image/video and annotation data
  - Expected sensor(s), mobile platform(s), mobile device(s), compatibility matrix for the front end mobile application to be developed
  - Data linkages to identify individual level data characteristics based minimally on eating occasion or meal, day, and week
- Develop a functional prototype system that includes

  - A front end mobile application to facilitate and control the collection and transfer of dietary images or video, and any associated information used within the system
  - Automated data screening and importation protocols for files transferred from the mobile application to a structured Dietary Rich Media Database
  - Software systems user-interface (web- or computer-based)
- Provide a report detailing planned analytic tools and resulting system capabilities for dietary intake summary data outputs. The analytic tools plan shall include justification for image processing algorithm source(s) selected or to be developed.
- Provide a report detailing output reporting systems feasibility, proposed timelines, data standards, and communication architecture for reporting dietary intake summary outputs to patients/subjects, electronic medical records, health surveillance systems, and researchers.
- Finalize database formats, repository structure, and data collection, transfer, and importation methods for targeted data inputs.
- Include funds in budget to present phase I findings and demonstrate the final prototype to an NCI evaluation panel.

Phase II Activities and Expected Deliverables:

- Beta test and finalize front end mobile applications listed in phase 1.
- Beta test and finalize automated file transfer, screening, and database importation protocols and systems.
- Develop, beta test, and finalize analytic tools listed in phase 1.
- Develop, beta test, and finalize applicable user interface systems.
- Develop and beta test output reporting systems capabilities for multiple system output targets listed above.
- Demonstrate system compatibility with sensor(s), mobile platform(s), and mobile device(s), included in the phase 1 compatibility matrix.
- Develop systems documentation where applicable.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.
- Usability testing for both front end and back end aspects of the user-interface.

309 Development of Low Cost, Small Sample Multi-Analyte Technologies for Cancer Diagnosis, Prognosis and Early Detection

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 4-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Cancer is recognized as a multistep process involving multiple genomic and epigenomic alterations that occur in multiple phases. The complexity of cancer requires multivariate assays for accurate diagnosis, prognosis and treatment monitoring. Recently, two multivariate gene-expression assays, Oncotype DX and MammaPrint, have been developed for determining whether chemotherapy is necessary for breast cancer. The Oncotype DX analyzes the expression of a 21-gene signature by TaqMan RT-PCR. The MammaPrint microarray which measures the expression of 70 breast cancer genes as a signature, provides information about the likelihood of tumor recurrence and guides treatment.

Given the multivariate and heterogeneous nature of the disease, it is likely that the early detection and diagnosis of cancer will be based on multiple analytes. However, the currently available clinical multi-analyte technology platforms have many limitations, including the requirement of multiple biopsies and special specimen collection/storage process. Additionally, their processes are often slow, complex, labor intensive and with sup-optimal sensitivity. These factors contribute to the added cost which also limits their broad applicability. For example the current list price of both Oncotype DX and MammaPrint are over $4000 per sample.

While the various NIH and other Government (DOD, DARPA, NSF, NASA, USDA etc) programs are developing new cutting edge technologies, their focuses are not on commercialization, and these novel technologies have not penetrated into clinical use. This contract topic seeks to promote the development of such innovations in early detection and diagnostic technology to facilitate the commercialization of low cost, efficient multi-analyte technologies with optimal sensitivity for cancer early detection, diagnosis and prognosis. In particular, this topic requests the development of technologies that can obtain multi-analyte molecular information from small volume clinical specimens (e.g. core biopsy, fine needle aspiration, circulating tumor cells or FFPE sections). In addition, this contract topic encourages proposals based on improving both early detection and diagnosis of cancer from easily accessible samples (e.g. blood, sputum, urine, fecal) with low abundant cancer markers.

Project Goals:

The short-term goal for the project is to develop working prototypes of low cost devices or methodologies for multi-analyte analysis of small samples or easily accessible samples with low abundant cancer biomarkers. Long-term goals are to improve cancer early detection, diagnosis, prognosis and treatment monitoring by developing low cost, more efficient, and more sensitive devices or methodologies for multi-analyte detection and analysis. Additionally, this topic requests the development of technologies that can be used with small volume, small numbers of cells or low cancer biomarker abundant clinical specimens obtained through regular biopsy procedures (e.g. core biopsy, FNA), surgery (e.g. FFER sections) or minimally invasive methods (e.g. blood, sputum, urine, and fecal). The technology should be innovative and make use of recent advances in areas such as microfluidics, nanotechnology, multichannel imaging, and transducer technologies for biosensors including optical, electrochemical, piezoelectric, Field Effect Transistor, cantilevers or any other rapid multi-analytes transducers. These devices and methodologies should be more cost efficient than current ones (>5x cost reduction), have significantly improved sensitivity/specificity (>10x) and can be used with samples obtained from single core biopsy or FNA. Acceptable devices and methodologies should be able to analyze at least 30 markers (DNA, RNA, RNAi, or proteins) simultaneously within four hours. If the innovation includes an integrated device, the cost of the market ready device should be less than $15,000. Ideally, the input for the device should be core biopsy, FNA or any small clinical biopsy specimen and the output should be the profile of the markers. This solicitation also encourages developing non-invasive biomarker based technologies and available multi-analyte technologies and assays for cancer early detection.

Accepted devices or methodologies include, but are not limited to:

- Rapid sample preparation and multi-analyte concentration technologies for high quality DNA/RNA RNAi/protein/cell
- Multi-analyte amplification technologies for DNA,RNA, ncRNAs, RNAi, proteins, and glycoproteins
- Low-frequency mutation analysis (e.g. for multiple relevant genetic markers/mutations)

- Rapid DNA sequencing (e.g. for multiple relevant genetic markers/mutations)
- Advanced PCR techniques
- New protein or DNA/RNA/ RNAi labeling and label free technologies. Preference will be given to label free technologies
- Point of Care DNA, RNA or antibody microarrays
- Automated integrated system

Phase I Activities and Expected Deliverables:

- Development of the essential components of the proposed technology.
- Demonstration of the feasibility of the technological innovation (e.g. spiking relevant body fluids with cancer cells or using FFPE). The offer should include benchmarking studies against current technologies. When possible, material that requires IRB approval to acquire or study should not be used for phase I.
- Characterization of the variation, reproducibility and accuracy of the method.
- Provide NCI with a detailed report of the number of cells and sample size needed, potential biomarker panels for the technology, estimations of sensitivity, selectivity, the cost of producing the proposed devices and/or reagents, including an analysis/breakdown of vendors and/or sources of raw materials.

Phase II Activities and Expected Deliverables:

- Develop a prototype of the device or analytical tool incorporating the technology demonstrated in Phase I including automation, software and data analysis.
- Test the device with clinically relevant cancer biomarkers.
- Test with a sufficient number of patient samples in several laboratories to demonstrate concordance, clinical utility and advantages, with an appropriate consideration of statistical significance.

310 Simplified Tissue Microarray Instrument For Clinical and Research Settings (NIH Technology Transfer)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The capacity to present defined, pre-selected samples of archival tissue for immunohistochemical and in situ molecular analysis has revolutionized the development and validation of tissue-based biomarkers in research and clinical application. In the clinical setting, most new diagnoses of cancer use immunohistochemical assays of tissue samples to support the diagnoses, and these immunohistochemical assays must be carefully calibrated and validated. Tissue microarrays are the means for validating the accuracy of these tissue diagnostic assays. Tissue microarrays can present hundreds of tiny discs (range 0.6 to 3.0 mm) of human or animal tissue specimens, arranged in a grid on a single microscope slide. Currently available arraying tools are capable of fabricating hundreds to thousands of copies of one such slide. Arraying tools can be quite expensive (especially the automated tools) , complex, and require special training to operate and maintain quality. These tools are

therefore often beyond the resources of many laboratories that either have to settle for lower quality slides produced without instrumentation, or purchase slides from manufacturers or specialty labs. Thus, a need exists for a simple and inexpensive instrument for fabricating tissue microarrays in clinical settings and research laboratories.

In the research setting, a typical application of tissue microarrays is the analysis of several hundred breast tumor tissue samples from patients at different stages of disease development (normal tissue, in situ cancer, invasive cancer, metastases) to identify the specific step at which biologic alterations take place, as well as the frequency of these alterations. In another example, tissue microarrays can be constructed from tissue materials in a retrospective study design, where one can immediately correlate the expression of a molecular marker with poor prognosis or response to therapy. Furthermore, coupling with automated imaging platforms is possible, and multiple different tumor types along with normal tissues can be screened simultaneously.

Researchers at NCI have invented an instrument for manual construction of tissue microarrays that is projected to be more accurate and less expensive than currently available. The invention requires further proof of concept to establish reliability, accuracy, and precision, and development of a fully functional prototype capable of being manufactured in quantity.

This invention is the subject of issued U.S. Patent Number 7,854,899 and HHS Reference Number E-098-2004/0.

Project Goals:

The preliminary goal of this project is to develop a functional prototype capable of generating tissue microarrays using the described methods. The final product will be a modular system that will enable clinical and research laboratories to construct tissue microarrays on a routine basis. The long term goal of this project is to bring to market this simplified, low-cost instrument for tissue microarray construction to meet the needs and applications of researchers and clinicians as described below.

This is an NIH TT (Technology Transfer) contract topic from the NCI. This is a new program whereby inventions from the NCI Intramural Research Program (Center for Cancer Research, CCR) are licensed to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this contract topic shall work closely with the NCI CCR inventor of this technology, who will provide non-human tissue samples, as well as other reagents as needed. The inventor will provide assistance in a collaborative manner with reagents and discussions during the entire award period. Between the time this contract topic is published and the time an offeror submits a contract proposal for this topic, no contact will be allowed between the offeror and the NCI CCR inventor. However, a pre-submission public briefing and/or webinar will be given by NCI staff to explain in greater detail the technical and licensing aspects of this program (for further information, see http://sbir.cancer.gov/news/upcoming/). In addition, a list of relevant technical, invention, and licensing-related questions and answers (including those from the public briefing) will be posted, maintained, and updated online (http://sbir.cancer.gov/news/upcoming/) during this time period.

The awarded contractor will automatically be granted a royalty-free, non-exclusive license to use NIH-owned and patented background inventions only within the scope and term of the award. However, an SBIR offeror or SBIR contractor must negotiate an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention. An SBIR contract proposal will be accepted as an application for a commercialization license to such background inventions. Under the NCI NIH TT program, the SBIR contract award process will be conducted in parallel with, but distinct from, the review of any applications for a commercialization license.

Model license agreements are available at http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx#LAP. Certain terms of the model license agreement are subject to negotiation. Please contact NIH Licensing and Patenting Manager (Cristina Thalhammer-Reyero, 301-435-4507, thalhamc@mail.nih.gov) with further questions.

Licensing procedures will comply with Federal patent licensing regulations as provided in 37 CFR part 404. A further description of the NIH licensing process is available at http://www.ott.nih.gov/licensing_royalties/intra_techlic.aspx. NIH will notify an SBIR offeror or SBIR contractor

who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 8.5.

Phase I Activities and Expected Deliverables:

- Develop an instrument as instructed in U.S. Patent 7,854,899 with
  - Capacity of 100 samples on a single microscope slide for immunohistochemical analysis;
  - Controls for immunohistochemistry, as well as clinical assay validation;
  - Capable of fabricating replicate arrays.
- Develop improved prototype with component parts, including:
  - Optimized needle(s) material and design;
  - Optimized templates design and features;
  - A donor block holder;
  - A recipient block holder/alignment device;
  - A recipient block-recipient-holes template;
  - A recipient block core-placement alignment template;
  - A needle holder/plunger device.
- Process and cost estimates for manufacture of the minimum number of tissue arrayers to accommodate 10% of current market.
- Provide NCI with all data resulting from Phase I Activities and Deliverables.

Phase II Activities and Expected Deliverables:

A Phase II proposal will typically only be invited by NCI if the Phase I contractor has been granted a commercialization license via the process described above.

- Build prototypes of the tissue arrayer that incorporates the following:
  - A multi-recipient block tissue arrayer appropriate for research use.
  - Capable of daily run, large core, low multiplicity immunohistochemical controls.
  - Capable of immunohistochemical assay validation for use with samples of moderate core size and scalable multiplicity.
  - Capable of controlling the temperature of the donor block holder, the recipient block holder, and the needle.
  - Capable of fabricating arrays in substrates other than paraffin blocks including, but not limited to, other solid/semi-solid embedding substrates and frozen materials.
- Design, optimize and evaluate the Phase I prototype as well as alternative Phase II prototypes by using the devices to construct tissue microarrays using tissue samples and then using the resulting tissue microarrays for:
  - Immunohistochemical controls
  - Validation of immunohistochemical tests
  - Immunohistochemistry and/or *in situ* assays in a research setting.

- Demonstrate that the Phase II prototype can produce tissue microarrays of equal quality to those constructed with current technology, according to the following quantitative metrics:
    - Presence of 95% of cores of tissue in array design (in first sections)
    - Alignment of cores, with less than 10% displacement
    - Less than 5% of cores placed off of perpendicular to array face
    - Generation of an equal number of TMA sections compared to current technology (within 5%).
    - 95% of cores without carry-over tissue from previously placed tissue cores.
- Provide data on the use of the tissue microarray by research facility staff for routine analytic protocols and of staff training in using the prototypes, as compared to other comparably priced arrayers.
- Develop a robust and scalable process for the manufacture of the tissue arrayer produced in Phase I.
- Provide NCI with all data resulting from Phase II Activities and Deliverables.

311 High Throughput Isolation of Antigen Specific T-cells for Cancer Therapy (NIH Technology Transfer)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The adoptive transfer of autologous tumor reactive T lymphocytes (T cells) can mediate significant tumor regression and long term cures in patients with refractory metastatic cancer. Despite these important clinical findings, adoptive cell transfer has not become widely available for patient treatment. Obtaining tumor infiltrating lymphocytes (TIL), T cells associated with a tumor that can exhibit high tumor reactivity, usually requires invasive surgery, which can lead to post-operative complications and is not always possible for all patients depending upon the location of their tumors. A significant obstacle in extending this promising therapy to a broader range of cancer patients has been the availability of highly efficient *in vitro* methods to rapidly isolate and expand tumor reactive T cells from peripheral blood for therapeutic use. Due to the low frequency of these T cells in the peripheral blood of cancer patients, isolation of these cells has traditionally been a difficult and laborious process requiring prolonged culture times and large amounts of reagents and equipment. Furthermore, the T cells typically generated during this protracted *in vitro* process develop unfavorable traits making them unsuitable for cancer therapy.

To overcome this significant challenge, intramural NIH investigators have invented a novel high throughput *in vitro* platform using quantitative RT-PCR (qPCR) as a functional screen to rapidly detect and isolate a variety of low frequency tumor reactive T cell clones from the peripheral blood of cancer patients (U.S. Patent Application No. 61/027,623). This novel technology has allowed the investigators to isolate and expand unique human T cells under GMP conditions that otherwise would not have been feasible. The utility of these inventions has been demonstrated by their application in isolating rare T cells and expanding them for human cancer therapy in an NCI sponsored clinical trial (NCI 08-C-0104).

This invention is the subject of U.S. Patent Application Number 12/866,919 and foreign counterparts in Europe and Australia (HHS Reference Number E-003-2008/0).

Project Goals:

The ultimate goal of this solicitation is to further refine and develop this novel T cell isolation platform into a standardized manufacturing operating procedure that could be commercialized for public and private use. The development of this technology would help overcome the fundamental obstacle of isolating highly tumor reactive T cells that circulate at low frequencies in the human body, which currently has prohibited the widespread use of adoptive T cell therapies. A current approach to obtain these low frequency tumor reactive T cells, such as TIL, from cancer patients is to use invasive surgical procedures to resect tumor and isolate TIL from the resected tumor. However, some tumors cannot be resected without risking patient mortality. The development of this current technology would provide patients with unresectable tumors another option for isolation of therapeutic T cells. If successful, this technology could potentially become the standard for tumor reactive T cell isolation and eliminate the need for the invasive surgical approach. The second long term goal of this solicitation is the development of novel applications for this T cell isolation platform, such as extending its applicability to other cancers and other disease indications. The awardee may have an opportunity to engage in collaborative research with NCI's researchers and benefit from current expertise in the field for preclinical development and the clinical application of the technology.

This is an NIH TT (Technology Transfer) contract Topic from the NCI. This is a new program whereby inventions from the NCI Intramural Research Program (Center for Cancer Research, CCR) are licensed to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this contract Topic shall work closely with the NCI CCR inventor of this technology, who will provide patient samples, necessary assay equipment, as well as other reagents as needed. The inventor will provide assistance in a collaborative manner with reagents and discussions during the entire award period. Between the time this contract topic is published and the time an offeror submits a contract proposal for this Topic, no contact will be allowed between the offeror and the NCI CCR inventor. However, a pre-submission public briefing and/or webinar will be given by NCI staff to explain in greater detail the technical and licensing aspects of this program (for further information, see http://sbir.cancer.gov/news/upcoming/). In addition, a list of relevant technical, invention, and licensing-related questions and answers (including those from the public briefing) will be posted, maintained, and updated online (http://sbir.cancer.gov/news/upcoming/) during this time period.

The awarded contractor will automatically be granted a royalty-free, non-exclusive license to use NIH-owned and patented background inventions only within the scope and term of the award. However, an SBIR offeror or SBIR contractor must negotiate an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention. An SBIR contract proposal will be accepted as an application for a commercialization license to such background inventions. Under the NCI NIH TT program, the SBIR contract award process will be conducted in parallel with, but distinct from, the review of any applications for a commercialization license.

Model license agreements are available at http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx#LAP. Certain terms of the model license agreement are subject to negotiation. Please contact the designated NIH Licensing and Patenting Manager (Samuel Bish, Ph.D., 301-435-5282, bishse@mail.nih.gov) with further questions.

Licensing procedures will comply with Federal patent licensing regulations as provided in 37 CFR part 404. A further description of the NIH licensing process is available at http://www.ott.nih.gov/licensing_royalties/intra_techlic.aspx. NIH will notify an SBIR offeror or SBIR contractor who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 8.5.

Phase I Activities and Expected Deliverables:

Platform Development:

- Develop protocol for T cell stimulation and growth in 384 well plate format to increase current throughput.
- Develop protocol for RNA isolation in 384 well format to increase current throughput.
- Develop 384 well multiplex qPCR assay for cytokine profiling.
- Apply automated liquid handling technology to facilitate high throughput screening.
- Apply automated liquid handling technology to facilitate T cell cloning.

Phase II Activities and Expected Deliverables:

A Phase II proposal will typically/generally only be invited by NCI if the Phase I contractor has been granted a commercialization license via the process described above.

Development of novel application:

- Epitope Discovery: Develop a novel high-throughput methodology to rapidly screen a peptide library of predicted peptides from putative antigen targets by analyzing their ability to stimulate human leukocyte antigen (HLA) matched human peripheral blood lymphocytes (PBLs).
- Utilize current platform to identify functional gene expression signatures for unique T cell populations.
- Isolation of novel T cell populations for human cancer therapy clinical trials.

312 Generation and Qualification of Site-specific Post-translationally Modified Proteins for Use as Calibrators in Pharmacodynamic (PD) Assays

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 3

Budget (total costs): Phase I: $150,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

NCI is committed to developing clinically useful biomarker tests that identify critical molecular targets within a patient's tumor, which can provide drug sensitivity, resistance, and real-time response information. For this SBIR topic, NCI requests that qualified small businesses submit proposals to aid the development of robust, quantitative pharmacodynamic (PD) immunoassays. Specifically, this topic solicits proposals to develop methods for the generation of stable, site-directed, high-content (50-80%) post-translationally modified (e.g., phosphorylated) protein calibrators AND associated processes for bench-top purification, characterization and qualification of these protein calibrators

Approximately 30% of proteins in eukaryotic cells are subject to phosphorylation. This crucial post-translational modification of proteins regulates numerous normal cellular events including the cell cycle, differentiation, metabolism, and neuronal communication. Likewise, dysregulated phosphorylation has been implicated in the etiology of many diseases. Thus, pharmacodynamic (PD) assays that directly detect and quantify phosphorylated proteins serve as a means to assess the type and magnitude of the cellular response to an external stimulus (i.e. cancer drugs). Given the important role kinases play, it is critical for researchers to have quality tools: (1) to generate stable post-translationally modified protein calibrators, particularly phospho-proteins; (2) to accurately identify the post-translationally modified sites; and (3) to quantify the level of site-specifically modified protein residues. Such reference standards are critically needed to serve as calibrators for absolute quantitation in PD assays. Moreover, the NCI anticipates that a subset of the PD assays that use these calibrators may ultimately be repurposed as companion diagnostic assays for approved drugs.

Producing post-translationally modified proteins (e.g., phospho-proteins) is currently imprecise involving chemical, enzymatic, and recombinant techniques. For example, biological systems provide poor control over site-directed phosphorylation and the percentage of phosphorylation at each site. A detailed characterization of the sites of post-translational modification is also difficult, with quantitation or semi-quantitation of modified residues now being carried out by mass spectrometry, fluorescence immunoassays, Microscale Thermophoresis (MST), FRET, Time-Resolved Fluorescence (TRF), fluorescence polarization, and ELISA. The development of technologies for producing high quality, high content, and analytically verified post-translationally modified proteins is becoming increasingly important for the systematic analysis of complex cell signaling networks that drive normal and abnormal cellular function. Thus, there is a great need to develop new approaches for quantitative generation and characterization of post-translationally modified proteins, which could encompass one or more of the methods above and be designed to be time-, labor-, and money-saving.

A primary roadblock in the development of robust, quantitative assays for the detection of post-translationally modified proteins is the lack of well-defined turn-key processes for the production and characterization of purified proteins that are quantitatively modified at particular amino acid residues but not others. (Such reference standards are critically needed to serve as calibrators.) Improving the quality of clinical grade assay development for post-translationally modified proteins will require the development of methods/systems that allow the reproducible generation of stable protein calibrators by directed and quantitative modification of certain residues (50-80% of the specified site), but not others (90-100% of the remaining sites should remain unmodified). Such methods and systems should be capable of evaluating the effectiveness of the post translational modification process, including an assessment of the heterogeneity of the modifications generated. The method/system should also be capable of assessing the effectiveness of the purification method(s), enabling both the detection of impurities and lot-to-lot comparisons.

The focus of this topic is to use innovative, state-of-the-art technologies to develop turn-key systems/processes that can provide assay-specific, stable post translationally modified proteins with reasonable throughput and the analytic verification of the particular modified residue(s) and level of modification. The desired outputs include reproducible production of post translationally modified protein calibrators, identification of the modified residue(s), 50-80% modification of the specified sites, purity, yields, and possibly other parameters (e.g., percent native vs. denatured protein). Easy-to-use, on-demand, bench top generation and characterization processes/systems will be applicable to a broad range of medical and biomedical applications in both academics and industry.

Thus, the overarching goal of this topic is to extend capabilities for the NCI and the broader cancer community to generate robust, quantitative protein-based assays to enable more efficacious, targeted therapeutic treatment of cancer patients.

Proposals submitted under this topic should include a detailed strategy/plan to develop the appropriate methodology, reagents, and instrumentation/processes to produce stable, high-content, site-specific, post-translationally-modified (e.g., phosphorylated) protein calibrators. Offerors submitting proposals under this topic are encouraged to consider focusing on the production of calibrators from the list of molecular targets below, which are of particular interest to the NCI. However, **proposals may focus on the development of any protein target and/or cancer-relevant post-translational modification of clinical relevance to cancer.**

Proteins/targets of particular interest to the NCI:

Receptor Tyrosine Kinases
MET
RON
EGFR
ALK
IGF1R

Non-Receptor Tyrosine Kinases
SRC
FAK
JAK

ABL
CSK

Project goals:

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development needs of the Institute and the broader cancer community. It is expected that companies submitting proposals under this topic will execute and extend their work to develop marketable instrumentation that enhances the qualification of critical protein reagents for use in PD and other types of diagnostic assays for cancer patients. The NCI Strategic Plan identifies validating molecular targets for cancer prognosis, metastasis, treatment response, and progression as a strategic priority (Strategy 4.2). Part of this strategy includes creating a library of validated molecular target assays to advance broad development of targeted anti-tumor agents. Assay development encompasses the provision of qualified critical protein reagents as capture and detection agents, calibrators, or controls. One reason for the slow adoption of PD and patient characterization assays is inconsistency in assay performance between sites, and a primary cause of this performance variability is the lack of qualified critical reagents. Market analysis indicates that qualified critical reagents are essential for rapid clinical adoption of new assays, especially the initial “home-brew” assays developed in CLIA-certified laboratories and in small biotechnology companies without the financial means to contract out reagent qualification. Development of technologies to include methodologies and/or prototype instrument systems for rapid, turn-key, bench-top generation of qualified post-translationally modified (e.g., phospho-protein) calibrators will be a valuable step toward the eventual commercialization of diagnostic assays that target post-translationally modified proteins associated with disease or drug action.

Phase I Activities and Expected Deliverables:

- Methodology, reagents, and instrumentation (if applicable) to produce stable site-directed, high content (≥50%) post-translationally modified (e.g., phospho-protein) calibrators or calibrators/controls
- Develop and deliver method, reagents, and a prototype instrument system (if applicable) that allows identification and quantification of site-specific protein modification
- Perform experiments and provide data that demonstrate reproducibility, variability, and accuracy of the technologies in comparison to reference materials and gold standard techniques for at least 5 of the designated targets, to include at least one receptor tyrosine kinase
- Deliver to NCI the generated calibrators and associated processes/technologies with applicable SOP(s) (Appendix 1) and Certificate of Performance(s) (Appendix 2)
- Deliver software (macros) for capture of data readouts and calculation of the requested variables
- Make available to NCI sufficient reagents and instrumentation to perform 10 test runs for independent validation
- Provide technical support and one on-site training session for NCI

Phase II Activities and Expected Deliverables:

- Processes should be optimized to generate quantitative, site-specific post-translational modification with the highest level of modification feasible (≥80% preferred), for all the designated protein residues of interest
- Refine and develop validated, CLIA-quality protocols, reagents and instrumentation systems (if applicable) with Quality Control and calibration protocols and standards for all analytic parameters for all of designated protein targets described in Phase I
- Perform full validation of the protocol and instrumentation prototypes with a statistically significant number of runs, and provide data that characterize reproducibility, variability, and accuracy of the refined

technologies [three lots of calibrators for all designated protein targets must be evaluated; all generated calibrators and the Certificate of Performances and SOPs of CLIA quality for use of the technologies and performance of all analytic characterizations are to be delivered to NCI (Appendix 1- 2)]

- Establish quality control measures and carryout critical reagent supply chain audits; evaluate the quality of supply chain for key reagents, materials, and instrumentation; provide data supporting consistent quality; and determine the accessibility to maintain supply chain
- Provide the NCI with access to the refined instrument(s) and sufficient reagents for 10 test runs of each analytic parameter for independent validation
- Provide technical support and one on-site training session for NCI
- Provide the program and contract officers with a letter of commercial interest

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with the tools and training they need to understand, detect, treat, and prevent a wide range of diseases. NCRR supports all aspects of clinical and translational research, connecting researchers, patients, and communities across the nation. This support enables discoveries made at a molecular and cellular level and through animal-based studies. These discoveries are translated to patient-oriented clinical research, with the ultimate aim of improved patient care. Through its programs, NCRR stimulates basic research to develop and provide access to state-of-the-art technologies and instruments for biomedical and clinical research; improves the public understanding of medical research; and provides information about healthy living. NCRR supports all aspects of clinical and translational research, connecting researchers, patients, and communities across the nation.

This solicitation invites proposals in the following areas.

015 Development of an Integrated Automated High Throughput Platform for Large-Scale Genetic and Therapeutic Screening in Zebrafish

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 1-2

Budget (total costs): Phase I: $400,000 for 6 months; Phase II: $1,500,000 for 2 years

Non-mammalian models, such as zebrafish, have emerged as powerful model organisms due to the availability of a wide array of species-specific genetic techniques, along with its short development time, fecundity and small size. For zebrafish larvae, their small size and optical clarity allows the use of powerful optical techniques that enable precise cellular visualization within the living animal, attributes that increase the ease of screening and allow screening on a large scale. Given the large number of zebrafish mutant and transgenic lines expressing fluorescent proteins, they can be utilized for large-scale chemical and therapeutic screens to identify lead compounds for drug discovery. Importantly, since the approach does not depend upon the prior identification of a target, it can be utilized to reveal novel insights and to dissect complex molecular pathways.

Despite the potential of the zebrafish for small molecule screens, very few have been reported and involve limited numbers of compounds. A key challenge has been the automated assessment of phenotypes because there are few image analysis methods capable of capturing the complexity of the whole organism. Additionally, throughput for zebrafish and other non-mammalian screens, for the most part, does not nearly approach that of high throughput screening (HTS) in cell culture systems. A principal hurdle to allowing more scientists to perform HTS using zebrafish is centered on the development of technology for automated image acquisition and data analysis. Although fluorescent microscopes with automated stages that allow examination of zebrafish embryos in microtiter plates have been developed, there are still many obstacles that impede optical access (e.g., pigmentation and the highly autofluorescent yolk sac), high-resolution image capture and analysis.

This contract topic seeks to stimulate research and development of a HTS automated system for imaging and analyzing zebrafish embryos and larvae that will be available commercially as a standardized, streamlined process, involving 2 or 3 pieces of equipment, requiring minimal laboratory space and that could be maintained and operated efficiently by a single person. Ideally, most of the process would be automated and all of the components listed below should be integrated into a single unified platform. Short of complete integration of all aspects, priority will be given to integration for each of two sub-groupings:

1. Microfluidic platform for automated sorting of zebrafish embryos and young larvae (e.g., mutant vs. wildtype) that will load directly into the wells of a screening microplate, pipette test substances into embryo-containing wells at appropriate final concentrations, allow for incubation ideally at 28.5°C and other temperatures, retrieve embryos from wells, read the signal in individual fish, and output data into an Excel spreadsheet format. Such an automated system must be able to distinguish between spurious maternal signal in the yolk and the zygotic signal in different tissues. Several sized screening microplates should also be developed to accommodate different stage embryos (e.g., gastrula vs. pharyngula vs. young larvae) for orientation in a defined orientation (e.g., lateral view) for image capture. If the embryo sorter can simultaneously genotype and score animals, it should be able to detect fluorescence for green, yellow and red regions of the spectrum and other numerous available fluorophores.
2. Image capture device for embryo high-throughput/high-content microscopy platform to quantify and report a comprehensive set of features such as count, length, area, intensity, and width, as well as general features about the embryo. The application should automatically discard analysis if the embryo is not in an optimal condition (wrong orientation, unhealthy, out-of-focus). Ideally, images of each embryo should be taken at 2.5x magnification, from one field per embryo down to an appropriate organ-sized field, and capture a variable number of optical sections (up to at least ten) through the embryo. The capturing device should have software to automatically stitch images together and score to exclude autofluoresce in the hatching gland and yolk.

Project goals:

The short-term goal of the project is to perform proof-of-principle technical feasibility demonstration of an automated system for sorting embryos and larvae, dispensing test substances, imaging and analyzing zebrafish embryos and larvae. The long-term goal of the project is the development of capabilities for higher throughput assays with ability to automate scoring of a visible marker or visible phenotype that will be available commercially as a standardized, streamlined process.

Phase I Activities and Expected Deliverables:

Phase I activities should support the technical feasibility of the approach. Specific activities and deliverables during Phase I should include:

- Design and construction of a prototype system(s).
- Validation of the prototype system(s) with a sponsoring NCRR investigator/laboratory to conduct usability testing. Include funds in budget to present phase I findings and demonstrate the final prototype to sponsoring NCRR investigator/laboratory or evaluation panel.
- Documentation providing a top-level description of the prototype system design(s), validation protocol(s), and testing results should be provided to NCRR as part of Phase I progress report.

Phase II Activities and Expected Deliverables:

Phase II studies should further refine the technology or strategy and test its effectiveness for incorporation into the research setting in terms of feasibility, cost, sensitivity, and specificity.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigation, and trials, observational studies, and demonstration and education projects. The Institute's

mission includes studies related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, blood, sleep disorders, and blood resources management. Studies are conducted in its own laboratories and by other scientific institutions and individuals supported by research grants and contracts. The NHLBI SBIR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

This solicitation invites proposals in the following areas.

044 Development of Induced Pluripotent Stem (iPS) Cell Lines for Use in Cell-based Bioassays

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-5

Recent technology enabling the production of induced Pluripotent Stem (iPS) cell lines has created significant opportunities for the development of new cell lines as products for use as cell-based bioassays such as in screening assays. The technology provides the means to expand the iPS cell lines to the numbers needed for bioassay applications and will enable the derivation of cell lines with specific phenotypic or genetic characteristics uniquely suited to specific assay requirements. Thus, iPS cell lines represent an excellent substitute for improving upon cell-based assays currently carried out with existing lines or limited supplies of primary cells. Basic research studies are needed to obtain sufficient quantities of the iPS cell line to test their suitability and for comparison to existing assay methods. And fundamental research to improve upon the methods used for iPS cell derivation will accelerate all commercial opportunities. The availability of the initial cell lines as products will benefit those investigators utilizing these assay tools in their research as well as serve as prototypes for investigators who may wish to develop new bioassays using iPS cell lines.

The goal of this solicitation is the development and production of new bioassays based on iPS cell technology to be used for research purposes and to be made available to the scientific community. The assays may be designed for basic research applications and potentially for future clinical assays. The derivation and expansion of the cell lines must be well defined and produced under appropriate manufacturing practices and quality control. The cell-based bioassay must be developed and validated including the use of existing assays as comparators. The successful applicant must develop a production plan to commercialize the assay.

Phase I proposals should focus on the development of a well-characterized iPS cell line and bioassay for research applications. Investigations in this phase will involve laboratory research and early scale-up studies.

Phase II proposals shall focus on scale-up and production of a bioassay for distribution. Assay validation will be required.

058 Novel Technologies for Powering Ventricular Assist Devices

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 4-5

Because the heart transplant donor pool in the United States is less than 2,500/year, ventricular assist devices (VADs) are the only realistic option for many late-stage heart failure patients. Currently, each year 2,000-5,000 receive VADs to bridge them to a heart transplant or as permanent (i.e. “destination”) therapy. However, the VADs currently available rely upon batteries that, despite recent advances, require frequent recharging, weigh on the order of pounds, and must be carried by the patient. Furthermore, the percutaneous cables used to connect the batteries and device controllers to the VADs provide a site for infection where the driveline crosses the skin. Consequently, the driveline site must be frequently cleaned to reduce the risk of infection.

Offerors will develop novel technologies for delivering power to VADs to successfully improve the quality of life and reduce the risk of infection associated with current methods for delivering power to VADs for chronic circulatory support. Examples of appropriate projects include (1) power and data transmission systems that do not require percutaneous drivelines and (2) innovative power sources which will reduce the size and weight of external batteries and the frequency of recharging them or, preferentially, eliminate external batteries altogether.

Phase I proposals should address initial development and feasibility testing of novel technologies for delivering power to VADs which can be applied to existing or new circulatory support devices. The technologies should have the potential to eliminate external batteries and/or percutaneous drivelines or make substantial improvements over existing power-related technologies for VADs so that the risk of infections is significantly reduced and the quality of life is improved. Preference will be given to proposals for technologies with the potential to eliminate external batteries and/or percutaneous drivelines.

Phase II proposals should be focused on completing the development of the technology such that it can be readily incorporated into circulatory support devices. The work is expected to include *in vitro* and *in vivo* studies to demonstrate effectiveness.

063 Reagents for Studying Human Lung Cell Biology and Cellular Function

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 4-6

Approximately half of the 44 cells that comprise the human respiratory tract still remain partially identified and their function(s) is incompletely understood (Franks et. al. Proc Am Thorac Soc 2008; 5: 763-6)). Suitable technologies are available to identify, sort, purify, culture, and determine cell surface markers or other unique identifying features that permit individual characterization of cell types. It seems feasible to unravel the origins and functional capabilities of lung cells involved in developmental stages of lung growth and in disease. But it will be necessary to generate new reagents that will identify these still incompletely characterized cells in the human lung, permit establishment of cell lines, and facilitate ready isolation from lung tissue.

Much is known already about many important cells in the human respiratory tract, but little is known about the supportive function of structural cells, the para-endocrine effect(s) of lung cells, and the location and functions of stem and progenitor cells that remain quiescent until stimulated to help repair tissue after injury or disease. Cellular functions that suppress or create apoptosis to reestablish normalcy need insight. Several examples are offered representing the three main compartments of the lung:

1. Among airway cells comprising the large and small airways of the human bronchial tree, the ciliated, columnar, secretory, and basal cells have been well studied, but more knowledge about epithelial stem and progenitor cells along the airways, mucus and ciliated cell interactions, functions of brush cells, and the stimuli from neuro-endocrine cells to affect integrity of the epithelium, all are needed.
2. In the alveolus, information is considerable about Type I cells, the multiple tasks of Type II cells, and surfactant production and properties, but Type II cell stimulated epithelial to mesenchymal transition is evolving but is not understood as a process leading to lung fibrosis, and the activity of interstitially located fibroblasts to secrete extracellular matrix needs more scrutiny.
3. The vascular bed of the pulmonary circulation needs study of the endothelial cells populating different locations and the capillary network, and interactions of endothelium with smooth muscle cells and with adventitial fibroblasts need examination.

Thus, special reagents are needed for studying lung cell biology and cells involved in organ development, growth, and disease. Examples of needed reagents include:

1. Antibodies that will recognize specific cell types and permit separation and recovery of cells from micro-dissected lung tissue.
2. Reagents to identify proteomic products produced by cells.
3. Antibodies that recognize cell surface markers that can help identify and track different cell lineages present in airway and alveolar structures.
4. Specific antibodies to recognize cell surface markers that help to separate out individual cell types from among heterogeneous lung tissue cells.

5. Reagents that track cellular changes in differentiation as development occurs, track cells that enter latency, and detect signals of re-stimulation or redeployment for repair tasks.
6. Reagents that characterize and identify “stem” and progenitor lung cells.

Phase I proposals should focus on development of reagents that identify unique cell surface markers or other special structures that would permit extraction of cells, considered to be incompletely characterized or identified, from human lung tissue biopsy specimens, or other lung bio-specimens such as transbronchial biopsy and bronchoalveolar lavage. This should lead to cell separation and establishment of *in vitro* cell cultures.

Phase II proposals should focus on scale up production of unique reagents for cell separation that can be placed in a repository for use by other investigators by application to investigate lung disease, and to study cell proteomics and other functions.

064 Novel Technologies for Assessing Lipoprotein Sub-fractions

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1-2

Identifying cardiovascular risk factors and understanding the contribution of those risk factors for cardiovascular disease is critical. Identifying individuals at very high risk for CVD and aggressive intervention are a critical factor to minimize the population wide CVD burden. Determining low density lipoprotein (LDL) as well as high density lipoprotein (HDL) particle size distribution may provide additional predictive power to LDL or HDL cholesterol measurement alone to estimate an individual’s risk for CVD. Current systems that can quantify the lipoprotein sub-fractions are labor intensive and need long turnaround time and thus are not practical for routine clinical applications.

Offerors will develop novel technologies for accurate, high throughput measurement of lipoprotein sub-fractions and use the developed technology to study the value of diagnostic performance in CVD.

Phase I proposals should address initial development and feasibility testing of novel lipoprotein sub-fraction measurements.

Phase II proposals should focus on the optimization and standardization of the technology and also compare with existing methods. It is expected that the developed technology be used to study the value of lipoprotein sub-fraction measurements in CVD risk assessment.

065 Computer Generated Diet and Exercise Reminders Promoting Cardiovascular Health

(Fast-Track proposals will be accepted)

Number of anticipated awards: 1-2

Research has shown that an individual’s cardiovascular health is improved with daily exercise and a healthy diet, and work productivity benefits from improved health status. Computer-based reminders have been shown to improve compliance with targeted tasks. By combining these two proven techniques, the goal of this solicitation is to improve the cardiovascular health of program participants through the development of a digital messaging service that intermittently sends heart-healthy nutritional tips and activity reminders to workplace computers. The service may send the information through a downloadable program or use ‘real-time’ push-type delivery. Message and prompt options may be personalized at registration.

Messages promoting cardiovascular health may include low-sodium, low-cholesterol and low-calorie food options or recipes (http://dashdiet.org/what_is_the_dash_diet.asp). Rotating dietary prompts may say: “Whole-grain bread or crackers may complement your lunch today”, “It’s time to drink some water” or “Make your snack a piece of fruit; it’s high in vitamins and fiber”. Audio/video demonstrations and/or text box pop-ups can offer suggestions to stretch, move, or engage in other easy-to-complete work-appropriate activities such as simple office yoga or isometric poses. Reminders may say “Get active, save your work and stretch your arms for 1 minute”, or “Reduce your risk for heart disease by making time for exercise; the stairs are a good alternative”.

The target audience includes computer users seeking to improve nutrition and or incorporate heart healthy activities into their day. The service must be 508 compliant and Federal Government IT security systems compatible. The National Heart, Lung, and Blood Institute will beta test the program and remain a recipient of free services after for-profit operations begin.

Phase I proposals should focus on prototype development. Product demonstration should be conducted half way into the contract. Small scale beta testing should be conducted 2/3rds into the contract to demonstrate feasibility.

Phase II should further refine the service, usability, usage metrics based upon continued user testing, menu options and technology, and will demonstrate effectiveness through end user appeal and lifestyle behavioral improvement success rates.

The program should include, but is not limited to:

- Offering the end user the ability to select the pop-up topic, delivery frequency and appearance.
- Collecting Phase I metrics to establish user opinion on subject matter, presentation, topic usefulness, program ease of use and general interest.
- Collecting Phase II metrics to evaluate program success and future directions.

066 Haptoglobin Treatment to Reduce Complications of Sickle Cell Disease

(Fast-Track proposals will be accepted)

Number of anticipated awards: 1-2

The release of hemoglobin into the circulation contributes to morbidity and mortality in intense hemolytic states such as sickle cell disease (SCD). Free hemoglobin related vascular reactivity, potentially through nitric oxide scavenging and oxidative stress associated with the iron moiety of heme likely result in pulmonary arterial hypertension, stroke and the acute chest syndrome in SCD. A glucocorticoid induced increase in haptoglobin synthesis in animal models has demonstrated an attenuation of the adverse clinical effects of free hemoglobin. (J Clin Invest [2009] 119:2271-80)

In SBIR Phase I, offerors are requested to establish a technical and scientific approach and demonstrate the feasibility of manufacturing a human plasma derived haptoglobin concentrate that is representative of the known human polymorphisms. The haptoglobin concentrate would be produced from plasma fractionation using established methodologies (such as Cohn or Kistler/Nitschmann methods) that could support scale-up in production to clinically relevant quantities.

The hypothesis to be tested in SBIR Phase II studies is that well-characterized, infused haptoglobin would complex with free hemoglobin and accelerate its clearance by CD163 on macrophages. This clearance should reduce the risk of altered vascular reactivity due to nitric oxide binding and similarly, reduce oxidative tissue damage mediated by heme iron. These possible effects will be tested in SBIR Phase II studies including a dose escalation safety study in human volunteers including determination of biomarkers which, if successful, could be followed by a trial to examine a dose response for painful events and/or the acute chest syndrome as clinical endpoints in individuals with SCD.

067 Transmit-receive Surface Array Coils for MRI of Patients with Internal Conductive Devices

(Fast-Track proposals will be accepted)

Number of anticipated awards: 1

Background

Magnetic resonance imaging (MRI) has the potential to guide non-surgical cardiovascular interventional procedures because it can visualize soft tissue, guide positioning of therapeutic devices, and assess treatment

outcome, all without ionizing radiation. To ensure that such procedures can be carried out effectively and safely it is essential to have devices (catheters, guidewires, etc.) that have the appropriate mechanical properties and that are conspicuous (visible) on the MRI images. The only general way to ensure conspicuity is by making the devices active, i.e. by making the devices capable of receiving NMR signals. Unfortunately, such devices (with conductive structures) can heat up considerably in a standard MRI scanner and this is one of the current major obstacles for MRI guided interventions.

The problem of heating of conductive structures during MRI extends to other applications such as imaging of patients with pacemakers and implantable defibrillators. A solution to this problem would have wide implications for the ability to scan a growing population of patients with implanted devices.

It has become clear that one of the key causes of active device heating is electrical coupling between the main MRI scanner transmit system (the body coil) and the devices. This coupling can be eliminated (or greatly reduced) by using a surface coil transmit system, which uses much smaller transmission coils than the main body coil of the scanner. There are two competing constraints that make it challenging to implement such a solution: a) For this solution to be effective the RF transmission system should illuminate the smallest possible area needed to effectively guide the procedure, and b) It may be necessary to follow devices over relatively large distances in the body. To accommodate both of these constraints we envision a surface coil transmit-receive array consisting of a relatively large number of smaller coil elements (i.e. 32, or more elements) covering the entire torso front and back (from the groin to the neck region). The system should allow dynamic activation and deactivation of coil elements such that only a subset of the transmit elements in the region of interest are active at any given point in time.

Specifications

- The coil array should cover the entire torso approximately 35 cm wide by 60cm long and the area illuminated by the transmission system at any given time should be controllable down to a size of 15x15 cm.
- It has to be possible to use the system with an MRI scanner without parallel transmit capability, i.e. the system has to be driven by a single RF waveform specified by the sequence. The system could include additional amplifiers and control hardware and software as needed.
- It should be possible to turn elements on and off dynamically. We envision a programmable interface that can be controlled from the MRI sequence environment.
- Ideally, it would be possible to control the phase of the RF pulse in each individual transmit element. Element-by-element RF amplitude control would also be desirable to enable dynamic RF shimming as needed to accommodate different body shapes and also to mitigate device heating through more advanced techniques.
- Multiple receive elements (~16 elements) must be active within the illuminated area to enable parallel imaging acceleration.
- The NHLBI currently uses 1.5T Siemens MRI systems and the proposed transmit-receive system must be compatible with these scanners (more details will be made available upon request).

Deliverables

Phase I should aim to provide a working prototype system that would allow a) MRI imaging with sufficient image quality to guide an interventional procedure , and b) comprehensive heating testing with interventional devices developed at the NHLBI. Heating test will be conducted in phantom and animal experiments at the NIH in collaboration with on-site scientists.

Phase II will incorporate design changes based on Phase I testing and deliver a complete transmit-receive system, which is safe for patient use. Specifically, the device should be eligible for designation as a “non-

significant risk device" by FDA or the vendor is expected to obtain an "Investigational Device Exemption" from the FDA.

068 Multilayer-coated Gratings for Phase-Contrast Computed Tomography

(Fast-track proposals will not be accepted)

Number of anticipated awards: 1-2

Background

In the United States computed tomography (CT) currently accounts for approximately 15% of all diagnostic imaging procedures. The number of CT scans has seen a threefold increase in the two decades leading to 2007 due to its unique capabilities. A CT scan produces high resolution, volumetric rendition of internal organs in a short period. CT scanners are relatively compact and economic to operate and maintain. Thus, they are widely available even in difficult environments. However, CT technology offers relatively low visibility (contrast) of soft tissue structures when compared to magnetic resonance imaging, and at the cost of exposing the patient to substantial ionizing radiation.

In the past few years there has been intense development of the concept of phase-contrast CT, a promising strategy to improve soft-tissue visibility and lower radiation dose by tenfold or higher over conventional absorption-based technology. To translate the phase-contrast concept to clinical applications, the technology must meet a number of requirements, including the ability to work with compact x-ray tubes, fast imaging speed and large field of view, and compact instrumentation. Full-field imaging techniques that utilize x-ray transmission gratings are prime candidates for eventual clinical applications due to their speed and adaptability, but they have not delivered the theoretically possible performance to-date. The main obstacle has been the inability to produce gratings of less than 1 micrometer periods for hard x-rays.

A promising technology to overcome the above limitation is vapor deposition of alternating high and low atomic number layers with layer thicknesses in the sub micrometer to nanometer range. The resulting multilayer structure serves as transmission gratings of extremely small periods when used in the transmission configuration. The concept has been proven effective in x-ray focusing optics. An additional advantage of this technology is that the grating depth-to-period ratio is unlimited in principle, making it effective for hard x-rays employed in animal and human CT. However, current multilayer x-ray transmission optics are fabricated on smooth substrates, while phase-contrast CT presents the need for deposition on patterned substrates in order to achieve sufficient grating areas for CT scanners. Therefore, the aim of this solicitation is to develop fabrication techniques of multilayer structures on patterned substrates to effect large-area, hard x-ray transmission gratings.

Specifications

This solicitation encourages the development of a directional deposition technology of multilayers of alternating high and low atomic number materials on periodic echelle (staircase like) substrates to form large-area x-ray gratings. Deposition rates of 200 nanometer per minute or higher are desired to permit total multilayer thicknesses of tens of micrometers in reasonable deposition time. The packing density of the layers should approach bulk materials for the purpose of effectively modulating the intensity and phase of hard x-rays used in animal and human CT scanners. The thickness and geometry of individual layers should be precisely controlled and uniform over the desired grating area. The directionality of the technology should be sufficient to target specific surfaces of the patterned substrates while avoiding deposition on other surfaces. Deposition protocols for material pairings of tungsten/silicon, chromium/silicon and titanium/silicon should be developed. Proper adhesion of the multilayer structure to the substrate should be achieved without spontaneous delamination. Individual layer thicknesses of approximately 50 nanometers and structurally uniform coated areas of 60mm x 60mm should be developed for small animal CT at 35 keV. Ultimately the technology should be extended to large area gratings for human CT scanners at 60 – 100 keV.

Deliverables

Phase I proposals should focus on the development of multilayer deposition technology of material pairings of tungsten/silicon for absorption gratings and chromium/silicon and titanium/silicon for phase gratings. The targeted x-ray energy is 35 keV for small animal CT scanners. The proposals should aim to achieve individual layer thicknesses of 50 nanometers, total deposition thickness of up to 100 micrometers, and structurally uniform coated areas of 60 mm x 60 mm. Techniques should be developed to selectively deposit on specific facets of the patterned substrate while minimizing material deposition on other surfaces. The substrates for coating tests will be provided by Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health (DIR/NHLBI/NIH). The proposals should also include evaluation of the multilayer structures with cross-sectional electron microscopy either independently by the contractor or with the help of DIR/NHLBI/NIH.

Phase II effort should focus on scaling up the technology developed in Phase I to larger grating areas and total deposition thicknesses of over 100 micrometers for human computed tomography.

069 Wireless Physiologic Telemetry for Interventional MRI

(Fast-Track proposals will be accepted)

Number of anticipated awards: 1

Background

Magnetic resonance imaging (MRI) has potential to revolutionize minimally invasive surgery and interventional procedures by affording improved tissue visualization without conventional surgical incisions. Many such procedures will be conducted under both X-ray and MRI guidance. Such procedures require high fidelity hemodynamic recording of physiological signals such as electrocardiography and invasive blood pressure, with seamless bidirectional transfer between X-ray and MRI. To date there are no suitable commercial solutions.

A wireless telemetry system would allow acquisition of hemodynamic signals (multichannel electrocardiography, invasive blood pressure, noninvasive hemoglobin saturation, temperature, etc.) safely in both the MRI and X-ray fluoroscopy environments, and allow continuous monitoring during transportation between the two.

Specifications

The system must conform to the following specifications:

- The system must operate safely at MRI field strengths of 1.0T to 3.0T.
- The system must record and transmit signals with the patient inside the magnet bore during imaging.
- The system should filter MRI-specific noise (e.g. radiofrequency pulses and gradient switching) and be robust to a range of rapid pulse sequences with continuous duty cycle, including single and multi-slice real-time, three-dimensional gradient echo, balanced steady state free precession, and (non-real-time) turbo spin echo techniques. The system must be able to filter noise from low frequency events, such as spoiler gradients or magnetization preparation sequences.
- The system should provide ten electrodes for diagnostic electrograms (four limb, six chest) under an X-ray environment and at least six (four limb, two chest) under an MRI environment. The electrode and lead system should be safe for operation under MRI, resistant to inadvertent loop formation, and should be radiolucent for operation under X-ray.
- The system should allow transduction of two simultaneous channels of invasive blood pressure from fluid-filled catheters, ideally with commonly used clinical invasive blood pressure transducers.
- The system should measure continuous noninvasive hemoglobin oxygen saturation.

- All physiological signals should be aggregated in a single unit for wireless telemetry. Signals must be received in at least one base station in each modality, (one in X-ray and another in MRI), with automatic handoff from one to the other. Base stations should connect to popular commercial hemodynamic recording systems (specifically Siemens Sensis and General Electric MacLab).
- The system should provide for uninterrupted operation for at least 6 hours.
- The system should NOT generate radiofrequency noise that interferes with MRI. The system should not interfere with common commercial Bluetooth and other common radiofrequency patient physiologic telemetry systems used during MRI.

Proposals to address electrocardiogram artifacts from magnetohydrodynamic effects are welcomed but not required.

The sponsoring NIH laboratory is willing to provide access to acquired physiological signals without preprocessing; alternatively the offeror should have access to such a laboratory independently for development and for testing.

Deliverables

The Phase I deliverable is a working prototype to support investigational X-ray and MRI guided interventional procedures in patients. This includes ten ECG leads for use in X-ray and at least six ECG leads for use in MRI, two invasive pressure transducers, and hemoglobin saturation.

The Phase II deliverable is a commercial-grade clinical system.

070 Bioabsorbable Stents for Pediatric Pulmonary Artery Stenosis and Aortic Coarctation

(Fast-track proposals will be accepted)

Number of anticipated awards: 1

Background

Mechanical stents to relieve obstructive cardiovascular lesions could have great utility in pediatric cardiology, but are unsuitable for small children. Commercially available stents limit vessel growth and require future surgical removal. Absorbable stents might revolutionize the treatment of congenital heart disease in children. Small children require small delivery systems for devices that are larger than adult coronary arteries. Specific target diseases include aortic coarctation and pulmonic stenosis, which currently require open surgical repair or multiple X-ray-guided catheter procedures in early childhood.

Specifications

These are transcatheter stents to be delivered using conventional interventional cardiovascular techniques including guiding catheters or sheaths, translesional guidewires, and balloon-expandable or self-expanding delivery systems. Conventional and novel approaches are welcomed.

Specific requirements of the stents include small delivery systems (5-6 French or smaller); sufficient radial force to resist elastic recoil for the two applications; sustained radial strength suited to the application for at least 3-6 months; controlled degradation within 6-9 months; inflammatory response that does not cause significant stenosis, restenosis, or aneurysm; resistance to downstream embolization or toxicity; and nominal calibers suitable for the most common lesions (pulmonary artery stenosis and aortic coarctation, see below) .

Proposed stent nominal geometry should be diameter (6-8mm), length (range 10-25mm), delivery system (5-6 French or smaller). The radial hoop strength of the deployed device should approach that of commercial balloon-expandable stent such as the Cordis Palmaz Genesis. Percutaneous vascular access routes for the pulmonary artery application include femoral and jugular venous. Percutaneous vascular access routes for aortic coarctation

application include transvenous-transeptal antegrade and retrograde transfemoral artery. The implant or the delivery system should be conspicuous under the intended image-guidance modality.

Deliverables

At the conclusion of Phase I, a candidate device design should be selected for clinical development based on *in vivo* performance of a mature prototype resembling a final design.

At the conclusion of Phase II, the offeror should obtain an investigational device exemption (IDE), and a supply of devices provided, for a first-in-human research protocol, involving at least 10 subjects, to be performed by the sponsoring NHLBI laboratory. The sponsoring NHLBI laboratory is willing to perform *in vivo* proof-of-principal experiments in swine, is willing to collaborate toward design of the clinical protocol, and is willing to provide clinical research services. The vendor is expected to perform or obtain safety-related *in vivo* experiments and data to support the IDE.

071 Electrophysiologic Catheters for Interventional MRI Ablation of Ventricular Tachycardia

(Fast-track proposals will be accepted)

Number of anticipated awards: 1-2

Background

Catheter-based ablation therapy is used to treat cardiac rhythm disorders. MRI may have value in targeting and assessing ablation lesions interactively during catheter based cardiac electrophysiology (EP) procedures. Real-time MRI EP ablation may be especially attractive to ablate mid-myocardial targets causing ventricular tachycardia in adults and children.

While technically feasible, there are no commercially available flexible catheter devices to perform EP ablation that are conspicuous and safe under real-time MRI guidance. Such technology, if commercialized, would enable novel treatments for ventricular tachycardia.

Specifications

The offering resembles a “conventional” deflectable multipolar catheter used to perform EP ablation procedures in geometry and in mechanical performance. These must be specified.

The offering must be conspicuous during MRI at 1.5T using “profiling” techniques such that positive contrast is provided along the entire intravascular device shaft and tip. The preferred catheter design for profiling is “active” such that the offering incorporates an intravascular MRI coil that allows the device and tissue to be imaged simultaneously. Alternative designs will be considered that provide high conspicuity during MRI.

The device must be able to obtain multi-channel local intracardiac electrograms. Suitable filtering functionality must be provided to connect the system to a commercial clinical EP recording and mapping system.

The device should be suitable for transcatheter endocardial application and for transthoracic intrapericardial epicardial application.

The device must be capable of radiofrequency ablation of ventricular myocardium during uninterrupted magnetic resonance imaging, which may require appropriate filtering. Alternative ablative energy sources may be proposed. Saline irrigation, or alternative target tissue cooling, should be integrated into the ablation system.

The device should interoperate during MRI with at least two other similar catheters that provide multipolar electrogram recording capability.

The offeror should consider capabilities to perform ventricular defibrillation in the MRI environment. The offering should operate with the interventional MRI system of the sponsoring NHLBI laboratory. The NHLBI currently uses 1.5T Siemens MRI systems and the proposed transmit-receive system must be compatible with these scanners

(more details will be made available upon request). The offering must be “MRI safe” or “MRI contingent” to allow future clinical procedures, without heating or local magnetic field disruption according to accepted industry standards and should be designed for safety in a clinical environment. Control of the system should be possible from a bedside operator and from a console-based operator outside the radiofrequency MRI system shield. The system should not generate radiofrequency noise that interferes with MRI at 1.5T. The system should be safe for operators and patients inside and near the magnet bores. The system should not interfere with common commercial Bluetooth and other common radiofrequency patient physiologic telemetry systems used during MRI.

Deliverables

At the conclusion of Phase I, a candidate device design should be selected for clinical development based on *in vivo* performance of a mature prototype system nearing final design lock.

At the conclusion of Phase II, the offeror should obtain an investigational device exemption (IDE), and a supply of devices provided, for a first-in-human research protocol, involving at least 10 subjects, to be performed by the sponsoring NHLBI laboratory. The sponsoring NHLBI laboratory is willing to perform *in vivo* proof-of-principal experiments in swine, is willing to collaborate toward design of the clinical protocol, and is willing to provide clinical research services. The vendor is expected to perform or obtain safety-related *in vivo* experiments and data to support the IDE.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The NIAAA supports research on the causes, prevention, control, and treatment of the major health problems of alcohol abuse, alcoholism, and alcohol-related disorders. Through its extramural research programs, the NIAAA funds a wide range of basic and applied research to develop new and/or improved technologies and approaches for increasing the effectiveness of diagnosis, treatment, and prevention. The NIAAA also is concerned with strengthening research dissemination, scientific communications, public education, and data collection activities in the areas of its research programs.

044 Development of Novel Compounds to Treat Alcohol Use Disorders

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

Efforts to develop medications for alcohol use disorders have expanded rapidly in recent years. Developing novel compounds for alcohol treatment is high priority for NIAAA Medications Development Program. Three agents directed at the addictive behavior in the use of alcohol —disulfiram, naltrexone, and acamprosate—are now approved for use in the United States and many other countries. Recently, topiramate has also been shown to be effective in treating alcohol-dependent patients. Still, these medications do not work for everyone. Because of this, further research is ongoing to develop more alcohol medications, perhaps producing medications that are more effective or at the very least, providing more choices for patients, similar to the situation for the treatment of depression with multiple antidepressants.

During the past decade, many new targets in the brain and liver have evolved that alter alcohol-seeking and drinking behavior. Brain effects and behavior may be influenced by agents directed at CRH1, adrenergic, opioid kappa, vasopressin V1b, NK1, orexin, NPY, NOP, glutamate mGluR2/3, mGluR5, GABAa α-1 and α-5 receptors. Several intracellular targets in additional (peripheral) organs have also been identified that alter outcomes of chronic alcohol use, including ALDH-2; PKC; PPARγ; epigenetic modulators, (HDAC inhibitors, methylases, demethylases, and microRNAs); rapamycin complex 1; and GDNF. Tissue damage induced by the influence of alcohol or acetaldehyde on any of the above have serious negative consequences including development of steatohepatitis, cirrhosis or hepatocellular carcinoma.

Specific areas of research include high-throughput screening for novel compounds, drug optimization, efficacy testing, GMP manufacturing, formulation, pharmacokinetic testing, and IND-directed animal toxicology. Any one of the following examples represents an area of interest to NIAAA but proposals are not limited to the examples given:

- Develop preclinically novel compounds that prevent or reduce drinking.
- Develop preclinically novel compounds that reduce or eliminate any of the multiple downstream negative consequences of alcohol use.
- Develop medications to reduce smoking in alcohol-abusing individuals.
- Develop novel medications to treat alcohol-induced organ damage by attenuating or reversing the tissue damage. Identifying new targets for drug development based on mechanisms underlying the alcohol-induced damage is encouraged.
- Screen available libraries of approved drugs for repurposing of drugs for any of the above indications.
- Advance personalized medicine by employing approaches of pharmacogenetics, sophisticated modeling of human characteristics, brain imaging and physiological and biochemical markers.
- Evaluate combinations of medications to increase efficacy with minimal side effects.

Deliverables would be periodic technical reports on the progress and activities carried out under these R&D contracts, final reports for Phase I and Phase II, and a summary of salient results including the results of all in vitro and in vivo testing in cells, animal and humans where applicable.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)

The NIDDK supports research in diabetes, endocrinology and metabolic diseases; digestive diseases and nutrition; and kidney, urologic and hematologic diseases. For additional information about areas of interest to the NIDDK, please visit our home page at http://www.niddk.nih.gov.

075 A Low Molecular Weight Thyroid-Stimulating Hormone Receptor Agonist for Thyroid Cancer (NIH TT)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 per year for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

NIDDK investigators have discovered and are evaluating the first potent and efficacious small molecule agonist of the thyroid-stimulating hormone (TSH, thyrotropin) receptor (TSHR) that has potential for clinical application in patients with thyroid cancer. This agonist drug is intended for use in patients for 2-5 days at a time following thyroidectomy and at subsequent intervals after initial treatment, when radioactive iodine screening is performed to detect the presence of remaining thyroid cancer cells.

Small molecule agonists and antagonists for G protein-coupled receptors (GPCRs) make up approximately 40% of the drugs currently in clinical use. The TSHR is a GPCR. The investigators have shown that this compound is active in model cell systems over-expressing TSHRs, in “normal” human thyroid cells (thyrocytes) in primary culture and, perhaps most importantly, after oral administration in mice to increase iodide uptake in the thyroid gland, similar to the protocol used for administration of recombinant human TSH (rhTSH, Thyrogen®, Genzyme Corporation) to patients with thyroid cancer. The ultimate goal is to see that an easily produced, orally administered, safe and effective drug is developed, launched, and used as an alternative to rhTSH in patients with thyroid cancer world-wide.

This invention is the subject of PCT Application No. PCT/US2008/011958, U.S. Application No. 13/125,045, and foreign counterparts in Europe, Japan, India, Canada and Australia (HHS Reference Number E-284-2008/0).

Project Goals:

The goal of the project is to obtain a full characterization of the small molecule TSHR agonist to support the filing of an IND application. The investigators have completed optimization for potency and selectivity using in vitro cAMP assays, have performed an SAR with the scaffold, have shown that one of the lead compounds is effective after oral administration in mice and have had 1 gram of a highly purified, active preparation of the compound synthesized. The investigators have recently determined the half-life in mouse plasma, the protein binding in mouse plasma and the degradation of the agonist by mouse liver microsomes. The investigators propose performing the following prior to the beginning of this contract: identification of the major metabolites and determination of their activities; pharmacokinetics in mice after intravenous, intraperitoneal and oral dosing of the parent compound and the major metabolite with measurements of their tissue concentrations; activity measurements in mice (including the major metabolite) with efficacy testing; and pharmacology in mice including cardiac, pulmonary and neurologic (hot plate) testing.

During the contract period the following will be performed in rats and dogs: determine pharmacokinetics and bioavailability; dose range finding; genetic toxicology; safety pharmacology; toxicology studies; and histology/pathology assessments. NIDDK will schedule a pre-IND meeting with the FDA and begin work on a formulation for administration to humans. If funded, we do not envision any roadblocks to accomplishing these steps.

This is an NIH TT (Technology Transfer) contract Topic from the NIDDK. This is a new program whereby inventions from the NIDDK Intramural Research Program are licensed to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this contract Topic shall work closely with the NIDDK inventor of this technology who will provide continuous guidance for the work performed by the offeror and perform in vitro laboratory analyses to support development of the agonist by the offeror. The inventor will provide assistance in a collaborative manner during the entire award period. Between the time this contract topic is published and the time an offeror submits a contract proposal for this Topic, no contact will be allowed between the offeror and the NIDDK inventor. However, a pre-submission public briefing and/or webinar will be given by NIDDK staff to explain in greater detail the technical and licensing aspects of this program.

The awarded contractor will automatically be granted a royalty-free, non-exclusive license to use NIH-owned and patented background inventions only within the scope and term of the award. However, an SBIR offeror or SBIR contractor must negotiate an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention. An SBIR contract proposal will be accepted as an application for a commercialization license to such background inventions. Under the NIDDK NIH TT program, the SBIR contract award process will be conducted in parallel with, but distinct from, the review of any applications for a commercialization license.

Model license agreements are available at http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx#LAP. Certain terms of the model license agreement are subject to negotiation. Please contact the designated NIH Licensing and Patenting Manager (Tara Kirby, Ph.D., 301.435.4426, tarak@od.nih.gov) with further questions.

Licensing procedures will comply with Federal patent licensing regulations as provided in 37 CFR part 404. A further description of the NIH licensing process is available at http://www.ott.nih.gov/licensing_royalties/intra_techlic.aspx. NIH will notify an SBIR offeror or SBIR contractor who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 8.5.

Phase I Activities and Expected Deliverables:

- Synthesize and evaluate activity of non-GMP drug in HEK293 TSH receptor cells and in primary cultures of retro-orbital fibroblasts provided by investigator.
- Conduct tests* in rats and dogs to determine pharmacokinetics and bioavailability.
- Conduct dose range finding* in rats and dogs with serum measurements of T_3, T_4, and thyroidal radioiodine uptake.
- Conduct genetic toxicology* in rats.
- Conduct safety pharmacology* in rats.
- Conduct toxicology* studies in rats for 5 days.
- Conduct histology/pathology* assessments in rats.
- Conduct Pre-IND meeting with FDA.

  *Note: Conduct as non-GLP or GLP as appropriate.
- Provide results of all studies.

Phase II Activities and Expected Deliverables:

A Phase II proposal will typically/generally only be invited by NIDDK if the Phase I contractor has been granted a commercialization license via the process described above.

- Conduct genetic toxicology in dogs.
- Conduct safety pharmacology in dogs.
- Conduct toxicology studies in dogs for 5 days.
- Conduct histology/pathology assessments in dogs.
- Develop formulation for administration to humans.
- Prepare IND application.
- Provide results of all studies.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This solicitation invites proposals in the following areas:

139 Confirming Compliance with Experimental Pharmacotherapy Treatment of Drug Abuse

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 2-3

Budget (total costs): Phase I: $150,000 for 6 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Assessing the results of clinical investigations of pharmacotherapies for treating drug abuse is made difficult by the lack of certainty that patients have taken the prescribed treatment as instructed. Negative outcomes of trials of pharmacotherapies might be due to the failure of patients to comply with the treatment. The outcomes of clinical trials are then uncertain, damaging the reliability of expensive clinical testing. Traditional bioassays (urinalyses of drug metabolites) are time-consuming and expensive. Therefore, NIDA seeks an accurate method/technology of compliance monitoring that is less expensive than bioassays and delivers monitoring results in a timely manner.

The technologies/products should allow patients to take experimental medications by the oral route in situations that are not supervised by clinical staff members (e.g. at home) yet provide relevant study staff with accurate, nearly real-time, knowledge of patient-specific compliance, thus allowing timely interventions that can correct noncompliance. It is envisioned that a flexible, multi-platform, mobile system could allow clinical researchers to accomplish the goals stated here.

Proposals concerning bioassays or biochemical testing methods are not of interest and will be deemed not responsive to this funding announcement. Systems requiring custom drug product formulation as an essential component of system operation are not of interest.

Phase I Activities and Expected Deliverables

Develop and test the feasibility of a prototype system demonstrating the following:

- Create new or adapt existing sensor or sensor system for detection of medication ingestion by a given patient. Examples may include video, voice or some combination of wearable psychophysiological measure sensors which in combination reliably indicate medication ingestion by the oral route.
- Create software as needed for reliably and securely storing data on the device as required.
- Create software as needed for reliable and securely transmitting sensor data to investigators including participant ID, time & date.
- Adapt existing database solution for reliable and secure storage and management of collected data compatible with mainstream data analysis solutions typically used in treatment research (e.g. Excel, SAS, or SPSS etc…).
- Create reliable and secure software solution for notifying patient and clinical trials staff of non-compliance within 6 hours and integrate it with a physical means of notifying the patient of non-compliance (e.g. patient wearable device, patient cell phone or study phone issued to the patient for use in the trial).
- Develop or adapt existing solution to verify patient identity; this may include developing tools for data analysis (such as image identity verification from sensed data) or peripheral tools such as a wearable RFID tag placed on the patient in the clinic and which will only permit transmission of data when the sensed data is within close range of the RFID (and hence is coming from the patient).
- Feasibility: test the software and hardware on patients in the lab receiving a medication and gather preliminary data on the reliability of the system and its ease of use by research staff and patients.

Phase II Activities and Expected Deliverables

Develop and validate a production model prototype by using the system in patients undergoing treatment with an FDA approved medication for treating addiction such as buprenorphine.

140 Development of a Solid Oral Dosage Form for Fenobam

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $150,000 for 6 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

Addiction to cocaine is a serious health problem in the U.S. (currently estimated by the U.S. Office of National Drug Control Policy at 3 million individuals). Untreated cocaine dependence significantly increases health, social service, and criminal justice costs to society and is a major vector contributing to the spread of infectious diseases such as HIV, TB, and hepatitis. To date, there is no FDA approved medication for the treatment of cocaine dependence. Responding to the need for effective therapies, the National Institute on Drug Abuse (NIDA) supports research and development activities regarding the preclinical and clinical aspects of pharmacotherapies for the treatment of cocaine dependence.

One of the candidate drugs to treat cocaine dependence is the mGluR5 antagonist fenobam. It is postulated that fenobam may be useful in the treatment of cocaine addiction because mGluR5 antagonists have been shown to affect four cocaine-induced processes thought to be important in the development of, and relapse to, cocaine addiction: 1) decrease in cocaine self-administration in rodents and in monkeys; 2) blockade of cocaine-cue induced drug seeking behavior; 3) blockade of cocaine-primed reinstatement in an animal model of cocaine self-administration; and 4) blockade of the acquisition of cocaine place preference in rodents. In addition, mGluR5 antagonists have shown efficacy in animal models of the same processes related to nicotine.

NIDA is planning to test fenobam for safety and efficacy in the treatment of cocaine dependence. As fenobam is an investigational compound which has not yet been approved for marketing in the United States, the development and manufacture of an appropriate oral dosage form of fenobam will be undertaken by NIDA. NIDA is, therefore, soliciting proposals for a SBIR contract for the development and manufacture of a solid oral dosage form (tablets or capsules) of fenobam under GMP conditions that will be used in IND-enabling non-clinical and Phases I/II clinical studies for the treatment of cocaine dependency. Fenobam is an insoluble drug in water and in common aqueous pharmaceutical solvents. There are very limited information on pharmacokinetics and pharmacodynamics of fenobam. Offeror is expected to develop a physically and chemically stable oral dosage form that demonstrates appropriate *in vitro* dissolution profiles and *in vivo* bioavailability in dogs and other appropriate animal models

Phase I Activities and Expected Deliverables

Offeror is expected to show the feasibility of solid oral dosage form(s) by demonstrating improved and optimized *in vitro* dissolution profiles of fenobam by applying pharmaceutical tools such as solubilization, complexation, solid solution, self-emulsifying delivery system (SEDDS), nanotechnology, etc. The offeror needs to develop methods for chemical assay of fenobam and *in vitro* dissolution at pH 1 and 7.4.

Phase II Activities and Expected Deliverables

Offeror is expected to formulate a prototype formulation(s) based on feasibility studies in Phase I and to perform bioavailability studies in dogs and in other appropriate animal models. The offeror is also expected to optimize the formulation(s) based on *in vitro* dissolution and bioavailability data in animals. The optimization process may be iterative. The offeror is expected to manufacture a GMP scale-up batch and to complete a CMC documentation for IND. The Phase II activities are summarized below:

1. Prepare prototype formulation(s).
2. Perform *in vitro* dissolution and *in vivo* bioavailability studies.
3. Optimize the formulation(s).
4. Collect stability data.

5. Manufacture a GMP batch.
6. Prepare product specifications.
7. Prepare Certificate of Analysis.
8. Prepare CMC documentations following FDA guidances.

141 Recovery Warrior: Behavioral Activation Video Game for Substance Abuse via a Commercially Available Active & Interactive Gaming Platform (e.g., Wii, Play Station Move, or Xbox Kinect)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $150,000 for 6 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Objective: This topic addresses the need for addiction treatment improvement by further developing and expanding an evidence-based therapy for use with in-treatment addicted populations through development of a commercializable and compelling game to be played over an "off- the- shelf" commercially available gaming system that can sense and be controlled through user body motions. Examples of systems at the time of this writing eligible for inclusion are the Nintendo Wii, the Sony Playstation Move and the Microsoft Xbox Kinect. The project will involve programming a "seek and destroy"- type of virtual interactive active game where patients find and use a variety of fun body movements over a natural user interface to eradicate virtual drugs, alcohol, and or cigarettes and related stimuli. The project may, depending on the console selected, also involve development of peripherals for use with the system.

Background

Recent research by Girard et al (2009) has shown that 4 sessions performing behaviors, incompatible with smoking cigarettes (crushing virtual cigarettes), within a virtual environment was more efficacious for smoking cessation than a similar game in which patients found and crushed virtual balls. The mechanism of this treatment is not well understood and it may be a form of extinction, counter conditioning, exposure with response prevention, or re-evaluative conditioning. Nonetheless, such virtual practice in a "game" environment may be uniquely helpful because it can deliver a large "dose" of alternative practice in a manner that people not just tolerate but also enjoy. The fact Girard et al's short duration gaming experience could improve outcomes in comparison with a "placebo" control suggests that games which involve the body in alternative practice may hold great promise for treating addiction.

Active, interactive videogames (AIVs) utilizing movement sensitive gaming consoles such as the Nintendo Wii, the Playstation Move, and the Xbox Kinect offer the opportunity for a substance abusers or smokers to put his/her entire body into the process of creating new sense memories with respect to substance-related cues. The opportunity to practice not responding automatically to such cues along with the opportunity to use many different muscle groups has potential to create new brain patterns that may disrupt old automatic behavior and emotional patterns and ultimately reduce relapse.

In addition to enhancing treatment effects for addiction and smoking cessation, AIVs may also be a form of health promotion to the extent that they get participants exercising. A prime barrier to smoking cessation attempts is fear of weight gain. An AIV-based treatment that increases large muscle group movement, thereby increasing metabolism and thereby reducing weight gain in smokers afraid to quit because of fears of weight gain is a further selling point for such a system.

One of the biggest challenges with both addiction and smoking cessation treatment is getting people to try existing treatments. Research indicates that many smoking quit attempts proceed without treatment, and less than 6% of quitters try both behavioral and medication treatment despite availability of recommended by experts

approaches. Addiction treatment utilization is poor as well with the majority of substance dependent people never accessing treatment. Novel treatments that appeal to people to enter and re-enter treatment and to stay in while enrolled may have dual benefits from both their own unique mechanism of action as well as by boosting exposure to the benefits of traditional treatment. Research has shown that tangible incentives improve outcomes of traditional treatments but they have been criticized for a lack of practicality and sustainability. It may be possible to use access to a novel treatment such as a videogame similarly, as an incentive for participating in or using a traditional treatment. The following scientific opportunity involves creating a highly engaging game which may have independent treatment effects and which when used in conjunction with traditional addiction and/or smoking treatment may help improve treatment engagement to leverage traditional treatment benefits.

Phase I Activities and Expected Deliverables:

- Modification of an existing game or development of a new therapeutic game for Wii, Move or Kinect, in which one or several participants hunt for and destroy virtual drug, alcohol, and/or smoking stimuli and paraphernalia using bodily movements sensed and recorded by the game;
- Development of peripherals for to interact with the game as needed;
- The game should include the opportunity for patients to select the substances that are most relevant to them or allow them to play a “multi-drug version” of the game if they need to address multiple substance use;
- The game should make use of a variety of body movements (e.g., stomping, shooting, batting, hurling, squashing etc…) to enable the participant to “virtually” destroy target substances as a way to “get clean” or win the war on their substance(s);
- The game should offer a variety of environments similar to those where addictive substances are used (urban neighborhood, bar, party), in which the patient can practice refusal skills as well as opposing practice;
- The game should include a variety of difficulty levels of increasing intensity and allow for up to 4 hours of gameplay;
- The game may include challenges in which participants refine skills for example, tossing the drug accurately into a trash receptacle that becomes smaller at each level, or kicking them through a goal;
- The game should be themed to pit the patient’s avatar who is the hero or “recovery warrior” against the substance of abuse;
- The patient’s avatar should be customizable to produce a likeness similar to the patient so he/she can name and view the avatar as him/herself; gender, height age, facial characteristics, race are some of the desirable customizable features;
- The game should be able to recognize and keep track of the patient’s performance over time so the patient can experience improvement in gameplay with each episode of practice;
- The game should record, store, and provide for downloading into a database, information regarding system use by each player such as time played, repetitions of behaviors and types of behaviors used to determine the extent of adherence and the “dose” required;
- The game may also allow participants to practice of drug refusal skills when faced with virtual drug offers; in games with this feature, virtual offerors should be responsive to the “recovery hero’s” actual body posture, gaze and physical or verbal responses and these should be displayed by the hero and offeror avatars within the virtual game;
- The game may allow for cooperation and interaction with other recovery warriors when the game is played as a group exercise;

- A pilot study with a group of adult substance users in treatment (N=9).
    - The study will expose patients newly enrolled in treatment to the game weekly for 30 minutes a session, for 4 weeks.
    - Measures collected at baseline will include weight, drugs of choice, and timeline follow-back.
    - Measures collected following each game exposure session will include acceptability, suggestions for improvement, AES/SAES craving ratings, urine drug screening and cotinine screening (for smokers) and treatment engagement data.
    - Measures collected 1 month after treatment entry will include timeline follow-back.
    - The pilot testing may be done in an iterative fashion so that multiple small focus groups are exposed to the program and it is modified in response to their comments.

Phase II Activities and Expected Deliverables:

Modification of a program, developed in Phase I, in response to customer feedback followed by an RCT Pilot clinical study evaluating the effectiveness of the Recovery Warrior Game. Outcomes collected will include AES, SAEs, treatment engagement information from clinic records, system use information (durations, movements repeated, times accessed) initial abstinence and/or smoking cessation rates via urine screening, smoking quit attempts, and weight changes.

142 Highly Effective Methods for Systemic *In Vivo* Targeted Delivery of shRNAi to the Brain for Treatment of Substance Use Disorders and Other Brain Disorders

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $150,000 for 6 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

There is a critical need to develop effective pharmacotherapies for substance use disorders (SUD). Currently, effective pharmacotherapies for cocaine and stimulant addiction do not exist and therapies for treating other substance disorders have limited efficacy. RNAi gene silencing technology offers new opportunities to develop safe and effective treatments for substance use.

The goal of this request for proposals is to address the need to develop highly effective methods for systemic *in vivo* targeted delivery on non-viral RNAi vectors to the brain to treat CNS disorders, including SUD. While significant obstacles remain to make RNAi therapy practical, improvements in delivery of RNAi to the nervous system will not only benefit the treatment of addiction, depression, psychosis, and brain cancers such as neuroblastomas and glioblastomas, but will also prove to be of interest to scientists conducting basic research on the nervous system.

RNAi has advantages over anti-sense RNA by using the endogenous enzymatic gene silencing mechanism instead of interfering with translation. Lower concentrations of RNAi than anti-sense RNA are needed to reach the cytoplasm of cell to prevent the expression of a gene and short length of RNAi molecules avoids triggering the innate immune system. The therapeutic application of RNAi to correcting dysregulation of signal transduction pathways and suppressing the effects of genetic mutation are limited by an effective systemic delivery system. A number of biological barriers must be overcome to deliver RNAi to its site of action, the cytosol. Systemic administration of naked RNAi is rapidly degraded by serum endonucleases and removed by glomerular filtration. The negatively charged properties of RNAi prevent crossing endothelial barriers such as the blood brain barrier. After crossing endothelial barriers RNAi molecules must diffuse to target cells where the RNAi molecule is internalized into endocytic vesicles by endocytosis. These endocytic vesicles fuse with endosomes which eventually become late stage endosomes that merge with lysozome. Here most RNAi molecules remain trapped

inside the endosome and become degraded in the lyszome, never reaching the RISC complex in the cytoplasm. Several strategies have been developed to overcome these biological barriers using non-viral siRNA vectors. These involves complexing the RNAi or shRNA (short hairpin RNA) with a cell penetrating peptide to assist in escaping entrapment of RNAi molecules in the endosomes, a ligand to target the cell type of interest, and in the case of the nervous system an antibody against the transferring or insulin receptor to permit transit across the blood brain barrier. Alternatively, RNAi may be complexed with dendromeres or linear cationic polymers. These cationic polymers form polyplexes with the negatively charged RNAi molecules. In the endosome these polymers act as proton sponges that cause the endosome to swell and burst to release the shRNA into the cytoplasm. These polyplexes can be modified to attach molecules that permit transit of the nanoparticles through the blood brain barrier and enable targeting of specific cell types. RNAi carried by non-viral vectors in most clinical trials is injected locally to the targeted tissue.

Currently, only two Phase I clinical trials with systemic injection of siRNAs to treat solid tumors are being conducted. To realize the potential of RNAi for the treatment of SUD and other brain disorders, systemic delivery of targeted delivery of RNAi carried by non-viral vectors will be the most tolerated form of therapy. Systemic injection of RNAi eliminates invasive injections that must be repeatedly delivered with the potential consequences of producing tissue damage and infection.

Project Objectives

The project objective is to deliver non-viral RNAi vectors to the cytoplasm of a cell type in the brain after systemic administration. Thus, the non-viral shRNAi vector must efficiently cross the blood barrier and efficiently deliver shRNAi to the desired cell type within the brain. After delivery to the target cell, shRNAi must efficiently escape from the endosome into the cytoplasm. The non-viral vector complexed with shRNAi should show no toxicity. Ultimately, the technology developed here will not only be applicable to the treatment of substance use disorder but to other brain diseases as well.

Phase I Activities and Expected Deliverables:

- Design and create non-viral shRNAi vectors for systemic administration to silence a gene in a defined cell type in the brain in a rodent model. Delivery may be oral, intranasal, intravenous, or intraperoteneal.
- Demonstrate that the selected gene in the chosen cell type in the rodent brain will be silenced *in vivo* by systemic delivery of the non-viral shRNAi directed against the selected gene.
- Demonstrate that an innate or adaptive immune response does not occur in response to chronic administration of the vector.
- Determine the pharmacokinetics, tissue distribution, and excretion of the shRNAi vectors.

Phase II Activities and Expected Deliverables:

Phase II studies will apply the delivery system created in Phase I to a potential therapeutic target for the treatment for substance use disorders.

For example, changes in G protein signaling have been shown to mediate addiction and relapse of drug seeking behavior. AGS3/GPSM1 activator of G protein signaling in the prefrontal cortex and core of the nucleus accumbens is upregulated during withdrawal following chronic administration of cocaine and heroin. The upregulation of AGS3/GPSM1 increases the amount of AGS3/GPSM1 binding to Giα and decreases the amount of Giα to interact with the βγ G proteins subunits, resulting in sustained ligand-activation of receptors coupled to βγ G proteins subunits such as mGluR2/mGLuR3, the DRD2 receptor, and the A2 adenosine receptor. Injection of an AGS3/GPSM1 peptide into the prefrontal cortex produced a cocaine sensitized phenotype manifested by enhance locomotor response to acute administration of cocaine. Injection of anti-sense AGS3/GPSM1 oligonucleotides prevented sensitization to cocaine and inhibited cocaine priming of drug seeking behavior by normalizing AGS3/GPSM1 protein levels. Injection of anti-sense AGS3/GPSM1 oligonucleotides into the core but not the shell of the nucleus accumbens also blocked reinstatement of heroin and ethanol seeking behavior. The

discovery of the process of RNA interference (RNAi) makes AGS3/GPSM1 a potentially therapeutic target for the treatment for substance use disorders.

- Implement a strategy to demonstrate that *in vivo* systemic administration of a non-viral shRNAi vector against AGS3/GPSM1 selectively silences AGS3/GPSM1 in DRD2 BAC expressing transgenic mice.
- Identify off-target silencing by the shRNAi against AGS3/GPSM1.
- Demonstrate that an innate or adaptive immune response does not occur in response to chronic administration of the vector complexed with AGS3/GPSM1 shRNAi.
- Determine the pharmacokinetics, tissue distribution, and excretion of AGS3/GPSM1 shRNAi vectors.
- Determine the dose response relationship for silencing AGS3/GPSM1 by the shRNAi/AGS3/GPSM1 vectors.
- Determine the duration of silencing produced by the shRNAi/AGS3/GPSM1 vectors.
- Demonstrate that systemic administration of the shRNA vector against AGS3/GPSM1 in rats and mice blocks conditioned place preference to cocaine and morphine and blocks the lowering of intracranial self-stimulation (ICSS) reward thresholds by cocaine and morphine.
- Demonstrate the effective of systemic administration of the shRNAi vector against AGS3/GPSM1 to block intravenous self-administration of cocaine and morphine and decrease the break point for self-administration of cocaine and morphine on a progressive ratio in rats and monkeys.
- Determine the dose response relationship for shRNAi vectors against AGS3/GPSM1 to decrease self-administration of cocaine and morphine in rats and monkeys.
- Determine the duration of suppression of i.v. self-administration of cocaine and morphine in monkeys following intravenous or intraperotoneall injection of the shRNAi vector against AGS3/GPSM1.

143 Feasibility of Development of RNAi-based Therapeutics for Treatment of HIV and HCV Infections in Drug Abusing Populations

(Fast-Track proposals will not be accepted.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Transmission between injection drug users (IDUs) is a major cause for HIV infection, accounting for around 25% of HIV new case. Highly active anti-viral treatment (HAART) is an effective treatment for HIV infection, and probably also effective in lowering the chance of HIV transmission among IDUs. However, poor adherence to lifelong HAART treatments, especially among IDUs, long-term side effects, and other factors dampen the effectiveness of chronic HAART. In addition, the therapy cannot eradicate the latent, low-level HIV reservoirs in patents.

When HAART is withdrawn from a patient, rapid HIV rebound occurs quickly. It is currently believed that a shorter-term, non-lifelong treatment that can achieve drug-free remission should be the new goal of HIV treatment. Patients with this type of treatment eliminate completely HIV completely from reservoirs in the body and would therefore alleviate the associated risk of spreading HIV through shared needles amongst IDUs.

Lentiviral-based gene therapy represents an optimal short-term treatment option that would eliminate all HIV viruses from the body. Whereas several research groups/companies have employed this strategy to deliver

multiple small-hairpin RNA (shRNA)/therapeutic components, all of them use *ex vivo* delivery methods and there is evidence that this approach does not eradicate the latent HIV reservoirs in patents.

New strategies such as *in vivo* delivery of Lentiviral-based multiple highly-potent small-interfering RNA (siRNA) and naturally-enveloped proteins of HIV could be developed to effectively treat more effectively HIV-infected IDUs especially those with latent reservoirs.

The burden of HIV and hepatitis C virus (HCV) co-infection is quite significant. In the United States, 15-30% of subjects infected with HIV are co-infected with HCV. Thus, NIDA also seeks the development of microRNA clusters designed to simultaneously inhibit several steps of the HCV cell cycle by specifically targeting various segments of the HCV gene as well as host cell companion proteins. This “cluster attack” on the HCV genome may particularly benefit human subjects who are co-infected with HIV and HCV because of the more severe nature of their disease and their more limited therapeutic choices. Combinatorial therapies, based on miRNAs, delivered via lentiviral vectors, may overcome the genetic barrier of concomitant and frequent HCV mutations. For example, the microRNA-mediated IFN-mimetic effect on the HCV cell cycle may deliver the on-target effects of IFN in the liver while avoiding the off-target effects of IFN in other tissues and organs.

Phase I Activities and Expected Deliverables

- Design and construction of potent shRNA vectors and *in vitro* assessments.
- Vector Packaging and Characterization.
- Assays for Inhibition of Gene Expression.
- Preliminary Toxicity Testing.

144 Smokescreen: Genetic Screening Tool for Tobacco Dependence and Treatment Approaches

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $150,000 for 6 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

A need exists to understand the genetic bases of tobacco addiction and related disorders. Advances in research supported by the National Institute on Drug Abuse (NIDA), and other NIH Institutes have identified several thousand genetic variants related to tobacco dependence. Given that genetic variants identified through these research programs, the research community is poised to take advantage of genetic technology that would allow researchers to use a single uniform platform for screening genetic variants related to substance abuse, and more specifically to tobacco dependence and related disorders.

The technology exists to develop a customized “out of the box” Smokescreen to screen thousands of an individual’s genetic variants at once. Development of this Smokescreen for tobacco dependence and related diseases would advance the understanding of the (1) genetic vulnerability to tobacco dependence, (2) gene variants related to co-morbidity, including risk and/or treatment approaches for other addictive and psychiatric disorders, peripheral artery disease, chronic obstructive pulmonary disease, and lung cancer, and (3) genetic profile of the patients for targeted treatments (i.e., pharmacogenetic approach).

Major limitations to studying how these genetic variations may be incorporated into personalized approaches for smoking cessation in the clinic include: 1) the small numbers of samples available from participants who have participated in clinical trials studying medications for treating tobacco addiction, 2) the lack of a universal and validated screening tool for data collection, and 3) the lack of a centralized database for storing and analyzing the

information into usable knowledge that clinicians and researchers studying tobacco addictions, its treatments and its consequences would reference.

This SBIR contract solicitation provides an opportunity to address these limitations. NIDA has identified a set of genetic variants that will allow the development of a uniform set of genetic variants to be screened. The overall goal is to encourage eligible small businesses to develop a genetic screening tool to profile specified genetic markers that may be related to smoking dependence and to smoking treatment, taking into consideration that the profiles of dependent smokers may be different than profiles of smokers responding to treatments for cessation. NIDA has established a prioritized set of genetic markers for developing the Smokescreen as described in: https://nidagenetics.org/neurosnp/neurosnp_about.html.

In order to collect clinical data for tobacco dependence and smoking cessation, a universal genetic "Smokescreen" is needed as a research tool for use in a wide variety of clinical settings, such as clinical trials, community treatment programs for smoking cessation, clinics specializing in tobacco additions, and researchers studying tobacco addictions, medications for cessation, and consequences of tobacco addiction.

A single genotyping or sequencing based platform for the genetic "Smokescreen" will be enriched for candidate SNPs/genetic regions that will provide a fourfold benefit to the clinical and scientific community: i) It will enable researchers to more accurately and reproducibly compare genetic variant data across studies; ii) it will provide a more focused and targeted SNP analysis that leverages existing knowledge; iii) it will be enriched with SNPs and/or targeted genetic regions from multiple ethnicities to allow for allele frequency differences and rare variations across populations, and iv) it will provide a resource for developing personalized approaches to pharmacotherapies for smoking cessation treatments and possibly other related co-morbidities, including risk and/or treatment approaches for other addictive and psychiatric disorders, peripheral artery disease, chronic obstructive pulmonary disease, and lung cancer.

The Smokescreen will provide patients and physicians with more information about the prospects for the smoking dependence risk (and possibly the other co-morbidities listed above) and it will support treatment decisions. The Smokescreen is envisioned to be used in conjunction with a nicotine metabolite ratio (NMR) test, as the NMR will likely be a better measure of smoking dependence. However, the Smokescreen may provide additional data for targeting cessation therapies by profiling or stratifying participants in clinical trials for smoking cessation medications, and may also be helpful for determining risk of potential consequences of heavy smoking, such as lung disorders and lung cancers.

Phase I Activities and Expected Deliverables

Prototype the Smokescreen for use in basic and clinical research settings with the most recent genetic technology available and using the prioritized genetic variants recommended by NIDA in https://nidagenetics.org/neurosnp/neurosnp_about.html (genotyping chip or new sequencing approaches such as MySeq from Illumina)

- Develop prototype Smokescreen that is "out of the box"
- Include a prototype approach for collecting the data and storing it for analysis, such as interfacing with a free, publicly accessible, central database for storing and analyzing the data with a user interface that is easy for upload and download of data, and create a database for researchers and clinicians to store and analyze the data from its use broadly, such as PharmGkb, GeneGo, Neuroscience Information Framework (NIF), or an alternative that integrates and expands the knowledge obtained from the use of the Smokescreen
- Analyze the basic and clinical research market for potential consumers of the Smokescreen

Phase II Activities and Expected Deliverables

Market and Manufacture the Smokescreen

- Market the Smokescreen for basic and clinical research use.

- Based on the market analysis, generate enough Smokescreens to be used for an initial phase of use to establish usability in terms of ease of use, data submission, cost and applicability in different research settings.
- Describe the necessary evidence that will be needed to validate the Smokescreen as a potential tool for use in a variety of indications, such as: smoking dependence risk, smoking cessation medications best suited for a given profile (combined with NMR), and risk for other diseases related to smoking.
- Develop methodologies that will:
    - Establish profiles that can be tested as to whether they predict smoking dependence, as well as smoking cessation;
    - Establish profiles that can be tested as to whether they predict other addictive and psychiatric disorders, peripheral artery disease, chronic obstructive pulmonary disease, and lung cancer.
- Market the Smokescreen for clinical application.

145 Feedback-regulated Naloxone Delivery Device to Prevent Opiate Overdose Deaths

(Fast-Track proposals will be accepted)

Number of Anticipated Awards: 1

Budget (total costs): Phase I: $150,000 for 6 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Drug overdose is currently the second leading cause of unintentional death in the United States, second only to motor vehicles crashes. The population at risk for opioid overdose is diverse and includes, for example, more than 3% of U.S. adults currently receiving long-term opioid therapy for chronic noncancer pain, in addition to drug/substance abusing population. Opioids are now more often being prescribed for patients with moderate to severe pain.

Thus, effective measures that would prevent/avert opioid overdoses are needed as overdoses and death often occur inadvertently in private settings where no one is present to offer assistance. Furthermore, patients with opioid addiction are prone to overdose on injected opiates or on excessive oral doses of opioid medications. These overdoses also often happen when no help is available and patient's lives are at risk.

The **objective** of this project is to develop an automated device that would administer standard doses of naloxone to a patient in overdose, thus reversing the effects of excess opiate. Naloxone has been used for decades in medical settings to avert opioid overdose, and recent pilot programs demonstrated the feasibility of proper use of naloxone by non-medical personnel. Patients expressing physiologic signals of opiate overdose (e.g. hypoxia, respiratory rate below a critical threshold for a critical period of time, etc.) could be administered an appropriate dose of naloxone even if unconscious. Due to the short duration of action of naloxone, the unit should be capable of repeating the injection after resetting itself and detecting another set of critical information.

There are more than 300,000 heroin users, nearly 5 million prescription opiate users, plus millions of chronic pain patients receiving end-of-life opiate analgesic pain care. The number of poisoning deaths and the percentage of these deaths involving opioid analgesics increase each year. From 1999 through 2006, the number of fatal poisonings involving opioid analgesics more than tripled from 4,000 to 13,800 deaths. Potentially, everyone who has been prescribed opioids, for pain or addiction, and heroin users, could be offered this device by their treatment provider who may be an addiction specialist, primary care physician or pain doctor. There is a crucial need to provide this device to these populations to prevent unintended overdose and deaths and to address public health need.

Phase I Activities and Expected Deliverables

- Design the prediction algorithm for opioid overdose requiring the intervention and establish the endpoints for algorithm development
- Design and assemble a prototype of detectors, injector and supporting hardware
- Propose a strategy to prevent un-indicated use, such as in a person who is unresponsive due to the reasons other than an opioid overdose
- Field-test the prototype with focus group participants.

Phase II Activities and Expected Deliverables

- Conduct the initial clinical testing in appropriate user population which is sufficiently powered to adequately inform Phase II
- Develop detailed plans for initial production model with cost projections
- Plan regulatory approval strategy
- Establish an FDA-compliant system
- Conduct clinical testing necessary for FDA approval.

146 Drugged Driving: Future Research Directions

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $150,000 for 6 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Drugged driving is a signature issue, one of the three top issues, of President Obama's 2010 Drug Control Strategy. Recently released NHTSA data from the 2007 National Roadside Survey of 7,500 daytime and nighttime drivers, including survey questions and oral fluid and blood samples, showed that 11% of samples had detectable levels of illegal drugs and 5% had medications. Several studies in the United States and European countries found that at least 35% of people stopped for erratic driving, drivers involved in a crash, and fatally injured drivers had at least one drug in their system, and many were under the influence of both drugs and alcohol. Marijuana is the most prevalent drug, after alcohol, found in samples from drivers involved in traffic accidents or stopped for impaired driving. Those and other released data have alerted the research community of the problem's magnitude and the urgency of addressing it.

Major effort to address the drugged driving problem will have a significant effect on the demand for drugs and on drug use in the United States. However, this effort is being impeded by multiple factors: 1) lack of available or quality data to adequately understand the magnitude of the problem and its possible solutions; 2a) lack of prevention strategies specifically tailored to drugged driving; 2b) lack of understanding of ways to tailor existing effective strategies to address drugged driving; 3) lack of treatment interventions to address the problem, other than from a criminal justice perspective: 4) lack of effective policy approaches to address the patterns of drugged driving problems.

This SBIR Contract solicitation seeks to address a need for more and better quality data on drugged driving and, therefore, seeks proposals to develop web-based systems that can allow for efficient access to and utilization of data on drugged driving, and allow public and private organizations and officials to locate, plan, implement and evaluate the effectiveness of prevention and intervention strategies to address the problem of drugged driving and its associated consequences. Responses to this solicitation can consider ways to adapt existing systems that

compile, organize and assess quality data and implementation approaches. They may also design completely new web systems to accomplish these goals.

The web systems proposed in response to this solicitation should provide a repository of necessary information and resources for researchers and policy-makers to utilize. Some of the core research questions to address through this scientific initiative include the following areas.

Data and measurement-specific questions:

- What data are currently available?
- How are these data collected?
- What are the important gaps in the currently available data?
- What strategies will help to fill these gaps?
- What methodologies could be used to improve the quantification of drugs?
- What standard screening methods can be developed for drug-testing laboratories?

Intervention-specific questions:

- What prevention or treatment interventions currently exist that directly address drugged driving?
- What existing prevention or treatment interventions that do not currently address drugged driving can be adapted to address drugged driving issues?

Policy-specific questions:

- How can the health care provided to individuals involved in drugged driving accidents be better managed?
- How can data and effective strategies be used to encourage states to adopt more effective drug laws?
- Which professional audiences need adequate information and training and what is the best way to provide this training? Examples might include law enforcement personnel, prosecutors, judges, health and education professionals, community practitioners, and parents and other family members.

Phase I Activities and Expected Deliverables:

1) Assemble a consultant team to determine available data sources and intervention strategies in regards to drugged driving.
2) Propose a prototype design for a web system to manage drugged driving data and to promote selection of appropriate prevention and intervention strategies.
3) Build a prototype for feasibility testing.
4) Conduct feasibility tests with a diverse array of professional audiences (less than 10 participants per professional group) – law enforcement, health professionals, and policy-makers. Focus group or user testing are possible approaches, but bidders are encouraged to be creative in their suggested approaches.
5) Analyze and report data.
6) Develop plan for Phase II activities.

Phase II Activities and Deliverables:

Pending positive results of Phase I design and feasibility testing,

1) Complete web-based tool.
2) Collect law enforcement and medical/health data to include in web-based tool.
3) Conduct a randomized study with professionals representing the target audience for the tool, primarily law enforcement, medical/health professionals and policy-makers, but also may include educators, service providers and others, to assess the tools ability to:
    a. Capture relevant and useful drugged driving data.
    b. Provide prevention and intervention information and other resources.
    c. Provide tools for the selection and implementation of prevention and intervention strategies.
    d. Provide information and other resources for assessment of implemented strategies.
    e. Capture and reassess trends in drugged driving data.
4) Close-out activities
    a. Analyze and report findings.
    b. Engage strategic partners for commercialization.
    c. Begin implementation of commercialization strategy.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

CENTER FOR GLOBAL HEALTH (GCH)

The Center for Global Health (CGH) leads the execution of the CDC's global strategy; works in partnership to assist Ministries of Health to plan, manage effectively, and evaluate health programs; achieves U.S. Government program and international organization goals to improve health, including disease eradication and elimination targets; expands CDC's global health programs that focus on the leading causes of mortality, morbidity and disability, especially chronic disease and injuries; generates and applies new knowledge to achieve health goals; and strengthens health systems and their impact.

CGH Internet site: http://www.cdc.gov/globalhealth/

For this solicitation CGH invites Phase I proposals in the following areas:

001 The Development of Lateral Flow Immunochromatographic Devices to Detect Antibodies

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: During the past decade, several companies have developed lateral flow immunochromatographic devices to detect antibodies to individual communicable diseases. More recently, these platforms have also been adapted to detect specific antigens associated with these infections. These inexpensive point-of-care (POC) tests offer considerable advantages over conventional laboratory tests, since they can be performed in remote, peripheral settings with little or no instrumentation by primary health care workers. In addition, counseling and treatment, if appropriate, can be given at the initial consultation. They have been used successfully to screen pregnant women for HIV and syphilis to prevent vertical transmission of these infections and therefore prevent congenital disease. In addition, in areas remote from formal, organized blood banks, these and other POC tests have been used to screen potential blood donors to prevent transfusion related infections. Unfortunately these

tests are usually performed as individual tests for antibodies or antigens for single infections, which results in a series of test strips being run in parallel. Each may have different flow characteristics, buffers and run times which can lead to confusion and potential inaccuracies.

Project Goal: The goal of this project is to develop a highly sensitive, highly specific, rapid and easy to use, disposable multiplex immunochromatographic screening device to detect Hepatitis BsAg and malarial antigen together with antibody to Human Immunodeficiency Virus 1 and 2 (HIV 1/2) and syphilis in a single finger-stick sample of whole blood in order to screen pregnant women to prevent vertical transmission of infection. In addition, a single device to detect Hepatitis BsAg and malarial antigen together with antibody to Hepatitis C Virus (HCV), Human Immunodeficiency Virus 1 and 2 (HIV 1/2) and syphilis in a single finger-stick sample in order to screen blood donors for transfusion- related infections in settings where conventional laboratory facilities are not available.

Vendors should have access to existing individual immununochromatographic tests to detect antibody to HIV, HCV and syphilis and tests to detect HBsAg and malaria. Likewise, vendors should be prepared to optimize their assays to detect both antibodies and specific antigens in the same cassette device on a single specimen. The contractor will be able to leverage this research and development opportunity to build capacity within the company to develop further multiplex platforms with antigen/ antibody combinations of diagnostic value. The CDC is willing to collaborate with small business by furnishing appropriate specimens to enable optimization of the multiplex platform and to facilitate both laboratory evaluations to be conducted within CDC laboratories in Atlanta and clinical evaluations in appropriate field sites in settings where these infections constitute a significant public health problem and where the tests would ultimately be used routinely.

Impact: It is anticipated that the development of these two multiplex immunochromatographic test cassettes could result in a significant reduction in rates of congenital HIV and syphilis together with other infections that can be transmitted from mother to child. In addition, make blood transfusions safer in areas where laboratory testing is either not available, or of poor quality.

002 Development of a Blood Donor Screening Test to Prevent Transfusion Transmitted Babesiosis

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Babesiosis is a potentially life-threatening zoonotic disease caused by intraerythrocytic protozoan parasites, which usually are tick-borne but are also transmissible by transfusion. Most infections are asymptomatic or only cause mild disease but severe disease can occur in neonates, the elderly and immunocompromised patients. Babesiosis became nationally notifiable in January, 2011.

Blood transfusion transmission of babesiosis, a healthcare acquired infection, has been recognized as an important source of infection and disease and is currently the most frequently reported transfusion acquired disease in the United States. Asymptomatic individuals are difficult to recognize and, therefore, transfusion of blood and blood components collected from them may result in transfusion-transmitted babesiosis (TTB), leading to potentially fatal clinical illness. Babesiosis is associated with significant morbidity and mortality. Increasing numbers of cases of TTB and TTB-associated deaths have been reported in recent years. In July, 2010 the Blood Products Advisory Committee of FDA strongly supported implementation of regional blood donor screening for *Babesia microti* infection. Currently, no blood donors screening test for babesiosis has been licensed and available diagnostic test formats are not suitable for the high throughput testing required for blood donor screening.

Project Goal: The goal of this project is the development, validation, and FDA clearance of a high-throughput method for Babesia- specific antibodies with sensitivity and specificity equal to or greater

than the existing gold standard method, the indirect immunofluorescence antibody assay, which is labor intensive and not suitable for high throughput blood donor screening. An effective and feasible test must be compatible with existing blood donor screening platforms, which require rapid results and flexibility to accommodate large numbers of samples tested simultaneously. Other innovative non serological approaches that can be easily integrated into existing blood donor screening platforms and workflows would also be considered. All submissions must include validation and FDA clearance as deliverables.

Impact: Reliable blood donor screening for babesiosis will prevent transmission by transfusion and decrease the number of deaths attributable to this healthcare acquired disease. This would preserve the blood supply since other options for control of this transfusion transmissible disease include stopping blood collections in risk areas for months when tick-borne transmission is occurring. Introduction of blood donor screening for babesiosis will help improve blood safety and prevent healthcare acquired disease, in keeping with CDC's goals. CDC will collaborate with test developers to validate tools in the field and to disseminate new technologies.

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

The mission of the CDC's National Center on Birth Defects and Developmental Disabilities (NCBDDD) is to promote the health of babies, children and adults and enhance the potential for full, productive living. To achieve its mission, NCBDDD works to: Identify the causes of birth defects and developmental disabilities; helps children to develop and reach their full potential; and, promotes health and well-being among people of all ages with disabilities, including blood disorders.

NCBDDD Web site: http://www.cdc.gov/ncbddd/index.html

For this solicitation NCBDDD invites Phase I proposals in the following area:

015 Development of an Assay to Rapidly Determine Folate Insufficiency in the Field

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Many neural tube defects (NTD), serious birth defects of the brain and spine, can be prevented if a woman consumes folic acid daily before and during early pregnancy. Although mandatory folic acid fortification has increased blood folate concentrations in the U.S., folate insufficiency remains a severe problem on a global scale. Determining the burden of folate insufficiency in a population can help set the stage for large-scale interventions such as food fortification. However, lack of data on blood folate levels hampers public health efforts to identify, intervene, and evaluate populations at risk for NTDs. In addition, many countries have remote and isolated populations, making population-based testing of blood folate levels challenging due to limited access to appropriate laboratories. Dried blood spots (DBS) might be adapted to assess folate status in the field, but use of this technique for collecting, storing, and analyzing folate levels quickly and effectively has not been established.

Project Goal: The goal of this project is to develop technology to measure blood folate levels, and specifically to develop: 1) an assay that can be used 'on the spot' in fieldwork either using DBS or whole blood, or 2) an assay in which the sample is collected in the field and analysis is done in a laboratory within 48 hours. Additional specifications are that 1) the instrument needs to be portable and low maintenance, so it can be used directly in the field; 2) the maximum volume needed should not exceed 50 uL of blood from a finger stick; 3) the imprecision of the assay should not exceed 10-15% at the clinical decision point of 140 ng/mL of red blood cell folate; and, 4) the assay results have to be comparable to traditionally accepted assays, such as the microbiological assay.

Impact: The global burden of folate insufficiency as it relates to NTDs has not yet been determined, but is estimated to be over 200,000 pregnancies yearly. This gap in data is primarily because large-scale national surveillance studies of folate levels and NTDs have not been possible in many countries. Additionally, many countries have remote areas where access to appropriate laboratory facilities is limited or available laboratories have limited capacity for biological testing. An assay that can add data on folate status from remote areas to a country's surveillance system can allow for an accurate burden of disease estimate. Development of these new assays would provide the means to document the folate status of target populations and help determine a course of action to address folate insufficiency programmatically. The expectation is that the proposed technology will meet market demand by laboratories and in-the-field research groups.

NATIONAL CENTER FOR EMERGING ZOONOTIC AND INFECTIOUS DISEASES (NCEZID)

The mission of the National Center for Emerging and Zoonotic Infectious Diseases aims to prevent disease, disability, and death caused by a wide range of infectious diseases. NCEZID focuses on diseases that have been around for many years, emerging diseases (those that are new or just recently identified), and zoonotic diseases (those spread from animals to people). NCEZID's work is guided in part by a holistic "One Health" strategy, which recognizes the vital interconnectedness of microbes and the environment. Through a comprehensive approach involving many scientific disciplines, NCEZID can attain better health for humans and animals and improve our environment.

NCEZID's Web site: http://www.cdc.gov/ncezid

For this solicitation NCEZID invites Phase I proposals in the following areas:

001 Vaccine Adverse Event Reporting System (VAERS) Application for Smartphone

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The Vaccine Adverse Event Reporting System (VAERS) serves as the nation's frontline early warning system to detect vaccine safety concerns. To enhance and sustain reporting efficiency and improve data quality during routine and emergency situations, recent efforts have been made to advance the VAERS web reporting interface and increase web-based reporting. Although web-based reporting can be done with handheld devices and smartphones it is cumbersome and time consuming. **The project goal therefore is the development of application software (app) that will help providers readily complete a VAERS reporting form from a smartphone or other device that will be uploaded instantly to the VAERS system.**

Currently, more than 200 million mobile apps are used by doctors and patients, and more than 600 million medical apps are projected to be used by 2012. A free app for the FDA's adverse drug reaction reporting system, "MedWatch", has already developed and marketed to health care providers and the public to facilitate reporting to MedWatch. With the rapid development of apps and increasing use and popularity of smartphones by health care professionals, an app to facilitate reporting to VAERS would likely be well accepted. This innovation relates to two CDC strategic public health priorities: 1) better prevent illness, injury, disability and death by enhancing the overall vaccine safety monitoring system and thereby keep vaccines as safe as possible and 2) strengthen surveillance, epidemiology, and laboratory services. Moreover, it also addresses the 2011 National Vaccine Plan goal to "enhance the vaccine safety system."

Project Goal: The goal of this project is the development of a smartphone application (e.g., iPhone, iPad, Android) that will allow a healthcare provider to instantly link to a VAERS reporting form that is user-friendly and is submitted to the VAERS central database rapidly and securely. This project is a proof of concept study that an app for smartphones can enhance reporting by providers. The VAERS app can include the

reportable event table, links to other Web sites and general information about vaccine safety. The results of this project have the potential to increase reporting for clinically important vaccine adverse events since it will target clinicians.

Further dissemination would require additional development to make the app compatible with other smartphones or devices. Collaboration with marketing venues will be necessary to make this app widely available (e.g., iTunes). Adding a link to download this app to multiple provider Web sites such as the American Academy of Pediatrics, American Academy of Family Physicians and others would be appropriate to widely disseminate and encourage adoption of this innovative technology.

Impact: This work will improve data quality, timeliness of data acquisition and data processing and augment (i.e., increase reporting from clinicians) the vaccine safety monitoring system that contributes to the assessment of risk from vaccinations and helps the Advisory Committee on Vaccine Practices (ACIP) and CDC make evidence-based recommendations for the use of vaccines. Enhanced reporting to VAERS will make this surveillance system a more robust and responsive public health tool for monitoring potential adverse event signals and lead to enhanced vaccine safety monitoring capacity.

002 Development of Rapid, Point-of-Care Tests for Diagnosis of Fungal Infections

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Fungi are some of the most common causes of major HIV-related opportunistic infections in the world. Cryptococcal meningitis is estimated to kill more HIV-infected persons than tuberculosis in sub-Saharan Africa. *Pneumocystis* pneumonia is the most common cause of acute pneumonia in most areas; histoplasmosis is extremely common in Central and South America, and penicilliosis marneffei is highly endemic in Southeast Asia. Prevention of serious sequelae (meningitis, respiratory failure, bloodstream infection) and death in these patients depends on prompt diagnosis and treatment. However, in many resource-poor areas, diagnosis of these infections is not possible because diagnostic tests are not available.

Project Goal: The goal of this project is the development of rapid, simple, affordable laboratory tests that are designed to be used in resource-poor settings to diagnose these diseases, and to distinguish them from other non-fungal diseases with similar symptoms. Such tests are feasible: a lateral flow “dipstick” test for *Cryptococcus* is in development and shows promise.

Rapid fungal diagnostics is an area that should be of particular interest to small business concerns. Laboratories in developing countries have either no alternative methods, or only elaborate and inefficient methods, to diagnose fungal infections at this time. The developed assays should have the characteristics of simplicity and robustness as described by the World Health Organization. Innovative approaches such as “dipstick” technology that can be used in the clinic and the field are already being employed in areas such as malaria diagnostics, showing proof-of-concept. Such rapid fungal diagnostics can be incorporated into resource-poor countries as laboratory capacity-building efforts develop and continue.

Impact: Rapid point-of-care tests can reduce deaths, hospitalization, and other serious sequelae (including immune reconstitution syndrome) among HIV-infected persons by differentiating these diseases from other clinically similar ones, thereby allowing for appropriate therapy. The primary benefit of such diagnostics is in resource-poor countries where HIV incidence is high, but market opportunities also exist in the United States where these fungal infections also occur in high-risk patient populations.

NATIONAL CENTER FOR HIV/AIDS, VIRAL HEPATITIS, STD, AND TB PREVENTION (NCHHSTP)

The mission of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) is to maximize public health and safety nationally and internationally through the elimination, prevention, and control of disease, disability, and death caused by HIV/AIDS, Viral Hepatitis, other Sexually Transmitted Diseases, and Tuberculosis.

NCHHSTP Web site: http://www.cdc.gov/nchhstp/

For this solicitation NCHHSTP invites Phase I proposals in the following areas:

031 Testing the Efficacy of HIV Prevention Strategies in Nonhuman Primate Models

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The field of HIV prevention has recently gained two new biomedical preventions: 1) a partially effective HIV vaccine, RV-144 delivered parenterally, and 2) partially effective pre-exposure prophylaxis (PrEP) in the form of a microbicide delivered as a vaginal gel, or as a daily, oral tablet. These preventions, while not yet approved for general use, are - either in the same form or in modified form - imminently scalable and likely to be implemented widely in upcoming years. CDC has been involved in evaluating and developing biomedical preventions such as these for many years, both in animal models and in humans. Historically, CDC has also provided guidance on implementation of vaccines, and through ACIP, will do so for HIV vaccines as they emerge.

It is likely that future HIV vaccine trials in humans will have to incorporate control arms with PrEP, be it by oral, vaginal or rectal delivery. The partial efficacy observed with a single intervention, whether it be a vaccine or PrEP, has escalated the need to assess if these two combined preventions will have additive, synergistic or possibly even negative/inhibitory effects. CDC researchers have used statistical models to explore these questions. However, animal models allow direct testing of the combined efficacy of partially effective prevention methods. CDC and the field of HIV prevention would gain immensely from such preclinical results. This could directly inform clinical trial designs, and also inform implementation of novel preventions.

Project Goal: The goal of this project is to model, in non-human primates, combination preventions such as PrEP and candidate HIV vaccines, to determine if these combinations have neutral, additive, synergistic, inhibitory or other effects.

Vendors should have prior experience testing animal models of HIV, anti-retrovirals or microbicides for HIV prevention and HIV vaccines. Proposals should include studies of at least 2 preventions for HIV infection (such as PrEP and a candidate HIV vaccine) that are representative of products in the current pipeline for human use. Furthermore, proposals should include a timeline, and should incorporate statistical estimates or sample sizes for different study arms that will allow appropriately powered evaluation of additive, synergistic or other interactions. Proposals may be structured to test study arms sequentially. Experimental design should include ways to measure correlates of protection and mechanisms of interaction. Studies should be designed with the long-term goal of providing information that will guide either human clinical trials of combination prevention, implementation of combination preventions or both.

032 Data Mining Software for Large-Scale Analyses of Infections Caused by Hepatitis Viruses

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The incidence of hepatitis A (HAV) is falling rapidly, but outbreaks of food-borne HAV outbreaks occur occasionally, and can involve large numbers of people. An estimated 50,000 Americans acquire new hepatitis B (HBV) infection annually. The health burden of persistent or chronic HBV infection is also heavy, with high mortalities due to cirrhosis or cancer. Adding to the burden of 1.2 million people in the USA estimated to be chronically infected with HBV is an estimated 40,000 foreign-born, chronically infected persons per year resulting from immigration. Chronic HBV causes liver cancer, and this cancer is a leading cause of death for certain population groups in the USA such as Asian-Americans. Hepatitis C (HCV) is the most common chronic blood borne infection in the United States, affecting 3.2 million of Americans. Since 2000, an estimated 85,000 new HCV infections occur every year and approximately 19,000 new infections occurred in 2006. However, 50% of HCV infected persons are unaware of their infection. Additionally, several studies have estimated that 30% of HIV-infected individuals are also infected by HCV and 60-90% of individuals infected with HIV by intra-venous drug use (IVDU) have HCV. The total estimate for co-infected individuals in the USA is 300,000. About a fifth of the American population is estimated to be exposed to hepatitis E (HEV), but the health impact of this exposure is unknown.

Hepatitis viruses are a diverse group of viruses with different major modes of transmission. Hepatitis A and hepatitis E viruses (HAV and HEV) may cause food-borne outbreaks. Hepatitis B and hepatitis C viruses (HBV and HCV) are blood-borne viruses. Although, infection with any of the hepatitis viruses has a similar clinical presentation, the degree of sequence heterogeneity of these viruses varies. Recent advances in laboratory technologies and computational biology have facilitated a comprehensive sequence analysis of the genomes of hepatitis viruses. This information allows for further refinement of molecular epidemiological approaches and provides opportunities to link molecular epidemiological data to demographic, clinical, laboratory and epidemiological data. In the course of engagement in clinical and surveillance studies and outbreak investigations, CDC generates, collects and analyzes such data. Because of the diversity in the type and sources of these data the CDC's seeks a software application that will be able to integrate these disparate datasets and that will permit data mining and investigator-initiated analysis.

Project Goal: The goal of this project is to develop data mining software that extracts, transforms, and loads structured data relating to infection with hepatitis viruses from diverse sources into a warehouse appropriate for mainframe, client/server, and PC platforms. This data will include but may not be limited to demographic, clinical, epidemiological, laboratory and phylogenetic information. The software will store and manage the data in a relational database system with a web-based interface to provide data access to the scientific community and analysis of relationships in the stored data using end-user defined queries to discover disease patterns and trends. The software will have hook interfaces which allow data to be exported to external programs for additional analysis, and capture those results into the database. The software will also export the outcomes of such analyses in publication ready formats.

Impact: It is expected that the software will generate associations between epidemiological and laboratory data leading to the discovery of new disease patterns, epidemiological trends and proteomic associations. Such discoveries are expected to lead to new strategies for public health interventions, surveillance, prophylaxis and the development of antivirals and vaccines. This software tool will be applicable not only to hepatitis viruses but other pathogens in the areas of epidemiology, laboratory research and public health.

033 Developing a Location-Based Application to Identify Adolescent-Friendly Health Care Services

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Adolescent births and sexually transmitted infections (STIs) remain serious public health issues in the U.S. Although the U.S. teen birth rate fell to an all-time low in 2009, it remains the highest among all developed countries. National data indicate that one in four adolescent females (14-19 years) has an STI. In 2007, 13% of high school students had been tested for HIV. Although adolescents have clear reproductive and sexual health care needs, it can be difficult to connect adolescents to sexual and reproductive health care that takes into account their unique needs. Confidentiality, transportation, hours of operation, and payment can all serve as barriers to referral to, and use of, appropriate youth reproductive and sexual health care. Schools can serve as an important source of referral to health care providers in the community, and evidence-based models such as that of *Project Connect* can help adolescents to access youth-friendly health care.

Project Goal: The goal of the project is to develop a software package featuring a location-based application that can be used on a cell phone or tablet to provide the location of adolescent reproductive and sexual health care providers local to the user. In addition, the application should have a web-based portal and SMS functionality (i.e., short message service, texting). The application would provide the name, location, and hours of service of the health care provider; contact information; services provided; fee for service and reimbursement options; transportation options; and directions. Additionally, health care providers would be screened for the extent to which their services are adolescent-friendly. Additional functionality may include the possibility of anonymous reviews and ratings by adolescents on service providers. Feasibility studies for this application would be conducted in Detroit, Michigan, and Los Angeles, California. Detroit is the site of a current replication of *Project Connect*, and Los Angeles was the original study site. Vendors should have expertise in sexual health among adolescents, school health, and sexual risk reduction strategies. Further, successful vendors will have expertise in youth usage of social media.

Extensive collaboration is likely for this project. This application overlaps with the STD and HIV testing site locator Web site in that it provides a listing of health care providers and locations and may extend the functionality of this Web site. Further collaboration would be done with *Project Connect* investigators and youth health care providers within community, school, district, and health departments in Detroit and Los Angeles. This research would benefit on-going efforts to link youth to care nationally and facilitate use of the *Project Connect* model, as well as to more effectively link youth to care in the selected cities.

Impact: This application would increase the effective referral to and use of reproductive and sexual health care resources for youth in metropolitan areas with high prevalence of HIV, STI, and pregnancy among adolescents. Broader use of a developed application would be used by youth, school health care providers, and community health care providers and would provide services that would prevent or provide care for HIV and STIs nationally.

OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE (OPHPR)

The Office of Public Health Preparedness and Response (OPHPR)'s mission is to strengthen and support the nations' health security to save lives and protect against public health threats. OPHPR has primary oversight and responsibility for all programs that comprise CDC's public health preparedness and response portfolio. Through an all-hazards approach to preparedness-focusing on threats from natural, biological, chemical, nuclear, and radiological events-OPHPR helps the nation prepare for and respond to urgent threats to the public's health. PHPR carries out its mission by emphasizing accountability through performance, progress through public health science, and collaboration through partnerships.

CIO's Web site link: http://www.cdc.gov/phpr/about.htm

For this solicitation OPHPR invites Phase I proposals in the following area:

001 Emergency Vehicle Proximity Alert System

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Motor vehicle injuries are a main cause of morbidity and mortality for first responders (police, fire, ambulance/EMT, and military), and delays in emergency response. Intersections are a frequent location for these incidents, with emergency vehicles approaching at a high rate of speed, often against traffic signals. Despite the use of sirens and flashing lights, other vehicles are not always aware that they are on a collision course with an emergency vehicle. Increasingly, many drivers may be distracted from the use of personal wireless electronic devices and are unaware of the sirens or flashing lights of first responders.

Project Goal: The goal of this project is to develop technologies to interface with personal wireless systems. These technology interfaces would enable first responders and other emergency vehicles to send out wireless messages (i.e., alerts to cell phones, GPS devices, etc.), located in private motor vehicles in the immediate vicinity of the responder. In addition to a proximity alert, this technology could also send wireless signals to vehicle based GPS devices showing location and direction of movement of emergency vehicles in relation to the private vehicle's GPS device.

Impact: Private driver situational awareness is critical to avoid vehicle crashes and related injuries associated with emergency vehicles transiting to or from emergency incident locations. The widespread use of wireless devices by drivers of motor vehicles will continue to increase as new technologies are developed in this market sector. Technologies that alert drivers of the proximity of emergency vehicles will reduce both morbidity and mortality of first responders as well as the general public. This technology will also increase response time and may result in more lives saved.

PART II HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT

1. INTRODUCTION

A Protection of Human Subjects section of the Research Plan is required for all proposals. The information provided in the section on Protection of Human Subjects should be consistent with the information provided on the face page of the application.

For all research involving human subjects, the Scientific Review Group (SRG) will assess the adequacy of protections for research participants against research risks, and the appropriate inclusion of women, minorities, and children, based on the information provided in the application.

To assist in preparing the section on Protection of Human Subjects, six possible scenarios are provided in Section 2 below. All research projects will fall into one of these six scenarios (to help determine whether research that involves the use of human data or biological specimens is human subjects research, refer to this Web site http://grants.nih.gov/grants/policy/hs). Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in Section 3 of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3, Definitions. Section 5 of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

2. SCENARIOS

Scenario A. No Human Subjects Research

If no human subjects research is proposed in the proposal, check the box marked “No” on the Proposal Cover Sheet (Appendix A) and indicate “No” on the Proposal Summary and Data Record (Appendix G). If your proposed research involves the use of human data and/or biological specimens, you must provide a justification for your claim that no human subjects are involved in the Protection of Human Subjects section of the Research Plan.

See the instructions for Scenario A.

Scenario B. Non-Exempt Human Subjects Research

If research involving human subjects is anticipated to take place under the award, check the box marked “Yes” on the Proposal Cover Sheet (Appendix A) and indicate “Yes” on the Proposal Summary and Data Record (Appendix G). Enter your Human Subjects Assurance Number.

In the Protection of Human Subjects section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46), and (2) the requirements of NIH policies on inclusion of women, minorities, and children. Research involving a clinical trial will fall under either Scenario E or F below.

See the instructions for Scenario B.

Scenario C. Exempt Human Subjects Research

If **all** of the proposed human subjects research meets the criteria for one or more of the exemptions from the requirements in the DHHS regulations (46.101(b)), check the box marked “Yes” on the Proposal Cover Sheet (Appendix A). Indicate “Yes” on the Proposal Summary and Data Record and insert E-1, E-2, E-3, E-4, E-5, or E-6 as appropriate, in the field for Exemption Number (Appendix G). Leave IRB Approval Date field blank since a Human Subjects Assurance Number is not needed for exempt research. Check “N/A” in field for “example of informed consent” and “Clinical Protocol” as these are not required for exempt research.

In the section on Protection of Human Subjects in the Research Plan, provide a justification for the exemption(s) containing sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate.

The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their Web site http://www.hhs.gov/ohrp/ for guidance and further information.

The exemptions appear in Part I, Section 3, Definitions.

Please note: If the proposed research involves only the use of human data or biological specimens, you should first determine whether the research involves human subjects. The exemptions do not apply if the research does not involve human subjects. For help determining whether research that involves the use of human data or biological specimens is human subjects research, please refer to this Web site http://grants.nih.gov/grants/policy/hs/.

See the instructions for Scenario C.

Scenario D. Delayed-Onset Human Subjects Research

If human subjects research is anticipated within the period of the award but plans for involvement of human subjects cannot be described in the application as allowed by the DHHS regulations (45 CFR part 46.118), check "Yes" to "This proposed project involves human subjects" on the Proposal Cover Sheet (Appendix A) and indicate "Yes" on the Proposal Summary and Data Record (Appendix G). In the section on Protection of Human Subjects in the Research Plan, you should either include an explanation of anticipated protections for human subjects or an explanation of why protections cannot be described.

Examples of delayed-onset of human subjects research include:

- Human subjects research is dependent upon the completion of animal or other studies; or
- Human subjects research protocols to be included will undergo an independent decision-making process (often defined by a FOA).

See instructions for Scenario D.

Scenario E. Human Subjects Research Involving a Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct a clinical trial during the project period, check the boxes marked "Yes" on the Proposal Cover Sheet (Appendix A) to "This proposed project involves human subjects," and "Clinical Trial?" Indicate "Yes" on the Proposal Summary and Data Record (Appendix G). In addition, complete the items regarding the Institution's General Assurance, Institution's Review Board, informed consent and clinical protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46);
2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
3) the ClinicalTrials.gov requirements if applicable;
4) the requirements of NIH policies on inclusion of women, minorities, and children; and
5) the requirements of NIH policy on reporting race and ethnicity data for human subjects in clinical research.

See instructions for Scenario E.

Scenario F. Human Subjects Research Involving an NIH-Defined Phase III Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct an NIH-defined Phase III clinical trial during the project period, check the boxes marked "Yes" to the following statement/questions on the Proposal Cover Sheet (Appendix A):

- This proposed project involves human subjects.
- Clinical Trial?
- Agency-Defined Phase III Clinical Trial?

Also indicate "Yes" on the Proposal Summary and Data Record (Appendix G) to the following question: Does this proposal involve human subjects research? In addition, complete the items regarding the Human Subjects Assurance Number, Institution's Review Board, informed consent and Clinical Protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46);
2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
3) the ClinicalTrilas.gov requirements if applicable;
4) the requirements of NIH policies on inclusion of women, minorities, and children;
5) additional Requirements for NIH-defined Phase III clinical trials; and
6) the requirements of NIH policy on reporting race and ethnicity data for subjects in clinical research.

See instructions for Scenario F.

3. INSTRUCTIONS FOR PREPARING THE SECTION ON PROTECTION OF HUMAN SUBJECTS

Scenario A. No Human Subjects Research Proposed

Criteria

Human Subjects Research	No
Exemption Claimed	No
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information

In the proposal narrative, create a heading labeled "Protection of Human Subjects" and include the following statement below the heading: "No Human Subjects Research is proposed in this proposal."

If proposed studies using human data or biological specimens do not involve human subjects as described in the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (http://www.hhs.gov/ohrp/policy/cdebiol.html), provide an explanation of why the proposed studies do not constitute research involving human subjects.

The explanation could include: a description of the source of the data/biological specimens, and whether there is any intervention or interaction with the subjects in order to obtain the specimens and data; what identifiers will be

associated; the role(s) of providers of the data/biological specimens in the proposed research; and the manner by which the privacy of research participants and confidentiality of data will be protected.

Research that does not involve intervention or interaction with living individuals, or identifiable private information, is not human subjects research (see Part I, Section 3, Definitions). Research involving the use of coded private information or biological specimens may not constitute human subjects research if the conditions of the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens have been met (http://www.hhs.gov/ohrp/policy/cdebiol.html).

Research that only proposes the use of cadaver specimens is not human subjects research because human subjects are defined as "living individuals." The use of cadaver specimens is not regulated by 45 CFR part 46, but may be governed by other Federal, State or local laws.

Scenario B. Non-Exempt Human Subjects Research

Criteria

Human Subjects Research	Yes
Exemption Claimed	No
Clinical Trial	No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct.

In the proposal narrative, create a section entitled "Protection of Human Subjects" and create a subheading for each of the following items.

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protections for Human Subjects - Section 4.1 - 4.1.4

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

Scenario C: Human Subjects Research Claiming Exemption 1, 2, 3, 4, 5, or 6

Criteria

Human Subjects Research	Yes
Exemption Claimed	1, 2, 3, 4, 5, or 6
Clinical Trial	Yes or No

NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct. The exemptions appear in Part I, Section 3, Definitions.

Although the research may be exempt from the DHHS regulatory requirements, it is still research involving human subjects and the application must follow the instructions that are identified for each of the following topics and provide the information that is requested.

In the proposal narrative, create a heading entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research falls under Exemption(s) … .”

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Justification for Claimed Exemption(s):

In this section, identify which exemption(s) (1, 2, 3, 4*, 5, or 6) you are claiming. Justify why the research meets the criteria for the exemption(s) that you have claimed.

If the research will include a clinical trial, even if exempt, include a Data and Safety Monitoring Plan – Section 4.1.5, and address the ClinicalTrials.gov requirements if applicable – Section 4.1.6.

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

*NOTE: If all the proposed research meets the criteria for Exemption 4, then the requirements for inclusion of women and minorities, targeted/planned enrollment table, and inclusion of children, do not need to be addressed.

Scenario D: Delayed-Onset Human Subjects Research

Criteria

Human Subjects Research	Yes
Exemption	Yes or No
Clinical Trial	Yes or No
NIH-Defined Phase III Clinical Trial	Yes or No

Instructions and Required Information

In rare situations, proposals are submitted with the knowledge that human subjects will be involved during the period of support, but plans are so indefinite that it is not possible to describe the involvement of human subjects in the proposal. The kinds of activities that lack definite plans are often institutional awards where the selection of specific projects is the institution's responsibility, research training grants, and projects in which the involvement of human subjects depends upon completion of instruments, animal studies, or purification of compounds.

If the involvement of human subjects cannot be fully described, create a heading entitled “Protection of Human Subjects” and provide a detailed explanation why it is not possible to develop definite plans at this time. The explanation should be specific and directly related to the Specific Aims in the proposal. If the involvement of human subjects depends upon information that is not presently available (e.g., completion of instruments, animal studies, purification of compounds), be explicit about the information and the factors affecting the availability of the information. Describe the information that will be necessary in order to develop definite plans for the involvement of human subjects, why that information is not currently available, and when the information is expected to become available during the course of the project.

If an award is made, prior to the involvement of human subjects the grantee must submit to the NIH awarding office for prior approval either (1) detailed information as required in the Research Plan, Protection of Human Subjects (addressing risks to the subjects, adequacy of protection against risks, potential benefits of the proposed research, importance of the knowledge to be gained, and data and safety monitoring plan if applicable) and certification of IRB approval, OR (2) if all of the research meets the criteria for one or more exemptions, identification of which exemption(s) is/are applicable to the research, and a justification for the exemption with sufficient information about the involvement of human subjects to allow a determination that the claimed exemption is appropriate. For clinical research, the request for prior approval must also address the inclusion of women and minorities, the inclusion of children, and provide completed targeted/planned enrollment tables as required in the Research Plan.

Under no circumstance may human subjects be involved in research until approval is granted by the awarding entity, and certification of IRB approval has been accepted by the agency.

In the proposal narrative, create a section entitled Protection of Human Subjects and a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and EITHER provide as much of the information that is requested as possible; OR describe why it is not possible to provide the information due to delayed-onset of human subjects research:

Protection of Human Subjects - Section 4.1 - 4.1.4

If the research will include a clinical trial, even if exempt, include a Data and Safety Monitoring Plan - Section 4.1.5, and address the ClinicalTrials.gov requirements if applicable – Section 4.1.6.

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

Scenario E: Clinical Trial

Criteria

Human Subjects Research	Yes
Exemption	Yes or No
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

In the proposal narrative, create a section entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research meets the definition of a clinical trial.” (See

definition of "clinical trial" in Part I.) Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - Section 4.1 - 4.1.6

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

Scenario F: NIH Defined Phase III Clinical Trial

Criteria	
Human Subjects Research	Yes
Exempt	No
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	Yes

Instructions and Required Information

In the proposal narrative, create a section entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research involves an NIH-Defined Phase III Clinical Trial.” (See "NIH defined Phase III Clinical Trial" in Definitions.)

Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - Section 4.1 - 4.1.6

Inclusion of Women and Minorities - Section 4.2

Additional Instructions and Requirements when NIH-Defined Phase III Clinical Trials are Proposed - Section 4.2.1

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

4. INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH

In your proposal narrative, **create a section entitled “Human Subjects.”** Although no specific page limitation applies to this section of the proposal, be succinct. Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the protection of human subjects. DHHS regulations and policies governing human subjects research are described and referenced in Section 5 below. **Use subheadings** to address the issues listed under items 4.1-4.4 below. If your research includes a clinical trial, include a subheading

"Data and Safety Monitoring Plan" and follow the instructions in 4.2 below. If your research includes an NIH-Defined Phase III Clinical Trial, follow the additional instructions in 4.2.1 below.

4.1 PROTECTION OF HUMAN SUBJECTS

4.1.1Risks to Human Subjects

a. ***Human Subjects Involvement, Characteristics, and Design***

- Describe the proposed involvement of human subjects in the work outlined in the Human Subjects Research section.
- Describe and justify the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
- Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention's dose, frequency, and administration.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

b. ***Sources of Materials***

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

c. ***Potential Risks***

- Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

4.1.2Adequacy of Protection Against Risks

a. ***Recruitment and Informed Consent***

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. If a waiver of some or all of the elements of informed consent will be sought,

provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. ***Protections Against Risk***

- Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:

  Additional Protections for Pregnant Women, Human Fetuses and Neonates:
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb

  Additional Protections for Prisoners:
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc
  OHRP Subpart C Guidance: http://www.hhs.gov/ohrp/policy/index.html#prisoners

  Additional Protections for Children:
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd
  OHRP Subpart D Guidance: http://www.hhs.gov/ohrp/policy/index.html#children

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

4.1.3Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

4.1.4Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

4.1.5Data and Safety Monitoring Plan

The NIH Data and Safety Monitoring Plan Policy is described and referenced in Section 5.3.

- If the proposed research includes a clinical trial, create a heading entitled "Data and Safety Monitoring Plan."
- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov/) and also see the following Web sites for more information related

to IND and IDE requirements:
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:
  a. PD/PI (required)
  b. Institutional Review Board (IRB) (required)
  c. Independent individual/safety officer
  d. Designated medical monitor
  e. Internal Committee or Board with explicit guidelines
  f. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.
- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). For additional guidance on creating this Plan, see the above reference.

4.1.6ClinicalTrials.gov Requirements

Public Law 110-85 (also known as the FDA Amendments Act (FDAAA) of 2007) mandates registration and results reporting of certain "applicable clinical trials" in ClinicalTrials.gov. Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)).

NIH encourages registration of ALL clinical trials whether required under the law or not.

Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Web site (http://prsinfo.clinicaltrials.gov/). A unique identifier called an NCT number, or ClinicalTrials.gov registry number, will be generated during the registration process.

The NIH implementation of FDAAA requires:

- the registration of applicable clinical trials in ClinicalTrials.gov no later than 21 days after the first subject is enrolled,
- the reporting of summary results information (including adverse events) no later than 1 year after the completion date for registered applicable clinical trials involving drugs that are approved under section 505 of the Food, Drug and Cosmetic Act (FDCA) or licensed under section 351 of the PHS Act, biologics, or of devices that are cleared under section 510k of FDCA, and
- if an “applicable clinical trial” is funded in whole or in part by an NIH grant or cooperative agreement, grant and progress report forms shall include a certification that the responsible party has made all required submissions to ClinicalTrials.gov.

For competing (new and renewal) applications that include applicable clinical trials which require registration and, in certain cases, require results reporting under FDAAA, provide the NCT number/s, Brief Title/s (protocol title intended for the lay public – see Definitions), and the identity (name, organization) of the responsible party (or

parties) and their contact information (e-mail address is required for internal administrative use only) in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov. If a new applicable clinical trial is proposed or if the contract will support an applicable clinical trial that is ongoing but not yet required to register under FDAAA (e.g. less than 21 days have passed since enrollment of the first patient), under the heading ClinicalTrials.gov include a clear statement that the application includes an applicable clinical trial which will require registration in ClinicalTrials.gov.

The entity responsible for registering the trial is the “responsible party.” The statute defines the responsible party as:

(1) the sponsor of the clinical trial (as defined in 21 CFR 50.3) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3), or

(2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that “the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements” for submitting information under the law) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).

For the complete statutory definitions of “responsible party” and “applicable clinical trial”, refer to Elaboration of Definitions of Responsible Party and Applicable Clinical Trial.

The signature on the application of the Authorized Organizational Representative assures compliance with FDAAA.

Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa).

4.2 INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the “Protection of Human Subjects" section. Although no specific page limitation applies to this section of the proposal, be succinct. The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described and referenced in Section 5.6.

Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the inclusion of women and minorities in clinical research.

In this section of the Research Plan, address, at a minimum, the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below in 4.3.) If using existing specimens and/or data without access to information on the distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion cannot be described (item 3 below). Alternatively, describe the gender and minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table in this section.
2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).
4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

A. ***One gender:***

1. One gender is excluded from the study because:
   - inclusion of these individuals would be inappropriate with respect to their health;
   - the research question addressed is relevant to only one gender;
   - evidence from prior research strongly demonstrates no difference between genders; or
   - sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.
2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. ***Minority groups or subgroups:***

1. Some or all minority groups or subgroups are excluded from the study because:
   - inclusion of these individuals would be inappropriate with respect to their health;
   - the research question addressed is relevant to only one racial or ethnic group;
   - evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
   - a single minority group study is proposed to fill a research gap; or
   - sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.
2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
   - the size of the study;
   - the relevant characteristics of the disease, disorder or condition; or
   - the feasibility of making a collaboration or consortium or other arrangements to include representation.
3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

4.2.1Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If the proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also must address whether clinically important sex/gender and/or race/ethnicity differences are expected from the intervention effect. The discussion may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. The discussion of expected sex/gender

and/or race/ethnicity differences in intervention effect must include selection and discussion of one of the following analysis plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, *or*
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), *or*
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups.

4.3 INSTRUCTIONS FOR COMPLETING THE TARGETED/PLANNED ENROLLMENT TABLES FOR REPORTING RACE AND ETHNICITY DATA FOR SUBJECTS IN CLINICAL RESEARCH

The NIH Policy on Reporting Race and Ethnicity Data for Subjects in Clinical Research is described and referenced in Section 5.8.

A. New Proposals

All new clinical research studies should collect and report information on participants with respect to two categories of ethnicity and five categories of race. The Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on the Office of Management and Budget (OMB) reporting standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

When reporting these data in the aggregate, investigators should report: (a) the number of research participants in each ethnic category; (b) the number of research participants who selected only one category for each of the five racial categories; (c) the total number of research participants who selected multiple racial categories reported as the "number selecting more than one race," and (d) the number of research participants in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed data should be compiled in a way that they can be reported using the required categories.

Instructions for Completing Targeted/Planned Enrollment Table

(http://grants.nih.gov/grants/funding/424/SF424R-R_enrollment.doc)

Provide the study title.

The "Total Planned Enrollment" means the number of subjects that are expected to be enrolled in the study, consistent with the definition in ClinicalTrials.gov.

The "Total Planned Enrollment" will be reported in two ways in the table: by "Ethnic Category" and by "Racial Categories."

"Ethnic Category": Provide the numeric distribution of the Total Planned Enrollment according to ethnicity and sex/gender in the top part of the table.

"Racial Categories": Provide the numeric distribution of the Total Planned Enrollment, this time by racial categories and sex/gender, in the bottom part of the table. Note that Hispanic is an ethnic, not a racial, category.

If there is more than one study/protocol, provide a separate table for each.

List any proposed racial/ethnic subpopulations below the table.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender using the Targeted/Planned Enrollment Table. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories.

If Data Collection is Ongoing, Such that New Human Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators should report ethnicity/race and sex/gender sample composition using the Inclusion Enrollment Report.

If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators should use the Inclusion Enrollment Report.

Research Conducted at Foreign Sites:

If proposed studies involve a foreign site, investigators are encouraged to design culturally sensitive and appropriate data collection instruments that allow research participants to self-identify their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the OMB-required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables that describe research in foreign sites, investigators should asterisk and footnote the table indicating that data include research participants in foreign sites. If the aggregated data only includes participants in foreign research sites, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign sites, the investigator should complete two separate tables – one for domestic and another for foreign participants.

B. Progress Reports

The Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) must be used for reporting accrual data to the NIH. In annual progress reports, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date, showing the distribution by ethnic/racial categories and sex/gender on the Inclusion Enrollment Report, and must update the Targeted/Planned Enrollment Table as needed.

4.4 INCLUSION OF CHILDREN

The NIH Policy on Inclusion of Children is referenced and described in Section 5.7. Instructions for this item under the “Human Subjects” heading of the Research Plan are as follows:

- Create a section entitled “Inclusion of Children” and place it immediately following the Targeted/Planned Enrollment Table.
- For the purpose of implementing these guidelines, a *child* is defined as an individual under the age of 21 years (for additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html).

- Provide either a description of the plans to include children, or, if children will be excluded from the proposed research, application, or proposal, present an acceptable justification for the exclusion (see below).
- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of children in the research project.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 CFR part 46 Subpart D (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd)) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section. It is expected that children will be included in all clinical research unless one or more of the following exclusionary circumstances apply:

1. The research topic to be studied is not relevant to children.
2. Laws or regulations bar the inclusion of children in the research.
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
    a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
    b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
    c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.
5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute/Center Director.

5. HUMAN SUBJECTS RESEARCH POLICY

Human Subjects Research Policy includes DHHS regulations for the protection of human subjects and the following NIH policies related to human subjects research.

5.1 PROTECTION OF HUMAN SUBJECTS

The Department of Health and Human Services (DHHS) regulations for the protection of human research subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. The regulations stipulate that the awardee organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in DHHS-supported research activities. The regulations require that offeror organizations engaged in nonexempt human subjects research supported or conducted by the DHHS hold a Federal-wide Assurance (FWA) with the Office for Human Research Protections (OHRP), and establish appropriate policies and procedures for the protection of human subjects. These regulations, 45 CFR part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html), Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852; telephone: 1-866-447-4777 (toll-free) or (240) 453-6900; e-mail: ohrp@osophs.dhhs.gov. In general, OHRP considers organizations that receive direct support from DHHS for the conduct of nonexempt human subjects research to be engaged in human subjects research (for more information on whether an institution is engaged in human subjects research, refer to: http://www.hhs.gov/ohrp/policy/engage08.html). When a research project is conducted by multiple organizations, each organization that is engaged in nonexempt human subjects research must hold an FWA and comply with the regulations at 45 CFR 46.

Nonexempt research involving human subjects may only be conducted under a DHHS award if the engaged organization(s) is operating in accord with an approved FWA and provides verification that an Institutional Review Board (IRB) that is registered under the specific FWA has reviewed and approved the proposed activity in accordance with the DHHS regulations. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the DHHS regulations. Foreign offeror organizations must also comply with the provisions of the regulations unless a determination of equivalent protections is made in accord with 45 CFR 46.101(h).

Under DHHS regulations to protect human subjects, certain research areas are exempt. However, if an offeror makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of an application or an application not being reviewed. The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. With the exception of research projects that meet the criteria for Exemption 4, studies that are exempt from the human subjects regulatory requirements must still address the inclusion of women, minorities and children in the study design.

Regulations of the Food and Drug Administration (21 CFR 50, 21 CFR 56) generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Additional information on FDA regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm. If work falls under FDA's regulatory requirements, the grantee must follow both DHHS and FDA human subject protection regulations.

The *National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* apply to all projects (NIH-funded and non NIH-funded) involving recombinant DNA molecules that are conducted at or sponsored by an institution that receives NIH support for recombinant DNA research. As defined by the *NIH Guidelines*, recombinant DNA molecules are either: (1) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or (2) DNA molecules that result from the replication of those described in (1). The *NIH Guidelines* set forth principles and standards for safe and ethical conduct of recombinant DNA research and apply to both basic and clinical research studies. The *NIH Guidelines* should be carefully reviewed and implemented to ensure that proper biosafety and containment practices are employed for all projects involving recombinant DNA research, including review by an

Institutional Biosafety Committee that meets the requirements of the *NIH Guidelines*. Further, the *NIH Guidelines* include special review and reporting requirements for the conduct of human gene transfer studies (under Appendix M). Failure to comply with the *NIH Guidelines* may result in suspension, limitation, or termination of NIH funds for recombinant DNA research at the organization or a requirement for NIH prior approval of any or all recombinant DNA projects at the organization. A copy of the *NIH Guidelines* is posted at the following URL: http://oba.od.nih.gov/rdna/nih_guidelines_oba.html and may be obtained from the NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892, 301-496-9838.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens, and medical information. Research involving existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered "research involving human subjects." The NIH Office of Extramural Research Human Subjects Web site contains additional information and Frequently Asked Questions to help investigators understand how these federal requirements apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

The DHHS regulations require the NIH to evaluate all proposals involving human subjects (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.120). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the proposal, or enter into negotiations to develop an approvable one.

5.2 VULNERABLE POPULATIONS

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners (or subjects who become prisoners after the research has started), or children, must follow the provisions of the regulations in Subparts B, C, and D of 45 CFR part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html), respectively. The subparts describe the additional protections required for conducting research involving these populations. Relevant information may be obtained at the OHRP Web site (http://www.hhs.gov/ohrp/policy/index.html).

REMINDER: DHHS regulations at 45 CFR part 46, Subpart C (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc) describe requirements for additional protections for research involving prisoners as subjects *or* individuals who become prisoners after the research has started. Refer to: http://www.hhs.gov/ohrp/policy/prisoner.html for complete instructions.

Exemptions 1-6 do **not** apply to research involving prisoners or subjects who become prisoners (see Subpart C (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc)). Although Exemptions 1 and 3-6 apply to research involving children (see Subpart D (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd)), Exemption 2 can only be used for research involving educational testing or observations of public behavior when the investigator(s) do not participate in the activities being observed.

5.3 DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. Prior to the accrual of human subjects, a detailed data and safety monitoring plan must be submitted to the offeror's IRB and to the funding entity for approval. Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other appropriate offices or agencies. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html). NIH policy specifically requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

5.4 IRB APPROVAL

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of a proposal. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html.

Following NIH peer review, the offeror organization will be notified of the need for review and approval of the proposed research by an IRB that is registered under the institutional assurance with OHRP. See http://www.hhs.gov/ohrp/ to register an IRB. Certification of IRB approval must be sent to the Grants Management Office identified in the notice requesting documentation. Certification of IRB review and approval must include: the PHS SBIR proposal number, title of the project, name of the program director /principal investigator, date of IRB approval, and appropriate signatures. Grantees may also use the optional form "Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule)" (OMB Form No. 0990-0263 http://www.hhs.gov/ohrp/assurances/forms/of310.rtf) to meet this requirement.

According to OHRP policy, in general, an institution is considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. See http://www.hhs.gov/ohrp/policy/engage08.html. All institutions engaged in human subjects research must obtain a Federalwide Assurance (FWA) from OHRP. Instructions for applying for a Federalwide Assurance (FWA) are available from the OHRP Web site at http://www.hhs.gov/ohrp/assurances/index.html.

DHHS human subject regulations at 45 CFR 46.103(f) require that each application for non-exempt HHS-supported human subject research be reviewed and approved by an IRB (see also http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html). Only the date of approval of the application should be submitted to NIH. However, the IRB must ensure that any corresponding protocol(s) are consistent with the application, and must maintain documentation of IRB approval of all corresponding protocols, including those reviewed by consortium participants. For multi-site research, the primary grantee is expected to collect the certification from each subrecipient.

Any modifications to the Research Plan in the proposal, required by either NIH or by the IRB, must be submitted with follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the PD/PI and the offeror organization to submit the follow-up documentation.

If more than a year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

5.5 REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified in PHS applications as senior/key personnel who will be involved in the design or conduct of human subjects research, before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following notices http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html, and Frequently Asked Questions at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm. Prior to award, offerors will be required to provide a description of education completed in the protection of human subjects for all senior/key personnel involved in the design or conduct of human subjects research. Although NIH does not endorse specific programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp for computer-based training developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

5.6 NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

NIH policy requires that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding IC Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other

circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The Research Plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5.7 NIH POLICY ON INCLUSION OF CHILDREN

Research involving children (see definition of "child") must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. Investigators should obtain full copies of the Policy and Guidelines from NIH staff, or from http://grants.nih.gov/grants/funding/children/children.htm.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, proposals for clinical research must include a description of plans for including children. If children will be excluded from the research, the proposal must present an acceptable justification for the exclusion.

The involvement of children as subjects in research must be in compliance with all applicable subparts of 45 CFR part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html) as well as with other pertinent Federal laws and regulations.

IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

5.8 NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH

The Office of Management and Budget (OMB) (http://www.whitehouse.gov/omb/fedreg_1997standards) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH) in OMB Directive 15, http://www.whitehouse.gov/omb/fedreg_1997standards. The standards were revised in 1997 and include two ethnic categories (Hispanic or Latino and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). Reports of data on race and ethnicity shall use these categories. The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The following definitions apply to the minimum standards for the ethnic and racial categories.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study.

Guidance on Collecting Race and Ethnicity Data from Human Subjects

When an investigator is planning to collect data on ethnicity and race, the categories identified above should be used. The collection of greater detail is encouraged, for example on ethnic/racial subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required categories. Use self-report or self-identification to collect this information by asking two separate questions – one on ethnicity and one on race. Collect ethnicity information first followed by the question on race and provide subjects with the option to select more than one racial category.

See NIH Policy on Inclusion of Women and Minorities and http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5.9 RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research on the transplantation of human fetal tissue is conducted, the offeror organization will make available, for audit by the Secretary, DHHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure DHHS access to those records, if maintained by an entity other than the offeror organization.

5.10 RESEARCH USING HUMAN EMBRYONIC STEM CELLS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research using human embryonic stem cells (hESCs) is proposed, the offeror organization will identify hESCs to be used from the NIH Registry (http://stemcells.nih.gov/research/registry/), or, if a specific cell line cannot be referenced at the time of application, certify that one from the NIH Registry will be used, in accord with the NIH Guidelines on Human Stem Cell Research (http://stemcells.nih.gov/policy/2009guidelines.htm) . See http://stemcells.nih.gov/index.asp for additional information on stem cells, and http://stemcells.nih.gov/policy/guidelines.asp for Federal policy statements and guidelines on federally funded stem cell research.

5.11 CLINICALTRIALS.GOV REQUIREMENTS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if the research includes an applicable clinical trial under Public Law 110-85, the offeror organization will be in compliance with the registration and reporting requirements of Public Law 110-85, if applicable (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). The law, enacted 09/27/2007, amends the Public Health Service Act to expand the scope of clinical trials that must be registered in ClinicalTrials.gov. It also increases the number of registration fields that must be submitted, requires certain results information to be included, and sets penalties for noncompliance.

The trials that must be registered are called “applicable clinical trials.” Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. NIH encourages registration of ALL trials whether required under the law or not.

Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa/).